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THE INFLUENCE OF HIGH PROTEIN FEEDING ON THE GENERAL METABOLISM, ON THE INTESTINAL FLORA AND ON THE BODY TEMPERATURE OF INFANTS*

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PART I.—GENERAL CONSIDERATIONS

L. EMMETT HOLT, M.D., AND P. A. LEVENE, M.D.

NEW YORK

A scrutiny of the extensive data obtained from the metabolic study of infants in a state of chronic malnutrition reveals the fact that the fundamental condition is a lack of utilization by the organism of nourishment. Despite the high calorific value of the diet, there is no increase in body weight. The cause of this imperfect utilization has not yet been established. It seemed to us that there was one possible factor, the study of which has been particularly neglected, namely: the correlation of the influence of intestinal bacterial flora and the utilization of the ingested foodstuffs. An investigation of this question was the original object of the work undertaken in this study. It was planned to alter the diet of the infants in a manner that in different periods it would contain a maximum of one of the three principal food constituents — protein, fat or carbohydrate — and a minimum of the other two. This plan was carried out in one series of observations. The infant was placed on a diet of modified milk containing 2.6 per cent. fat, 3 per cent. sugar and 2.4 per cent. protein. This was continued for about three weeks. It served to determine the normal flora for this child. The diet

*From the Laboratories of the Rockefeller Institute for Medical Research, and the Babies' Hospital, New York.

was then changed to a milk formula containing 0. per cent. fat, 6 per cent. sugar and 3.5 per cent. protein, and later to one with 2.9 per cent. fat, 1.5 per cent. sugar and 5.8 per cent. protein.

It was observed that under the influence of these changes in diet the bacterial intestinal flora was modified both qualitatively and quantitatively. The changes are described in detail in Dr. Wollstein's paper (Part III). The gratifying feature of the observations was the marked general improvement noted during the period of high protein intake. The general condition of the infant was better than in any of the preceding periods, and the stools acquired a normal appearance, which is so rare in conditions of chronic malnutrition and which in this patient they had not previously shown.

It was intended to repeat this study on a greater number of infants. However, an unexpected observation caused us to abandon the original plan of the work and direct our energies for the present toward the analysis of that observation. This was the abrupt development of fever and nervous symptoms during the period of high protein intake, under conditions which led to the suspicion that the food given might be the cause of these phenomena.

Finkelstein[1] was the first to revive the interest of the pediatrist and the general physician in febrile conditions that are caused not by infection nor by products of bacterial action. He observed that some of the fundamental food constituents that are essential for maintenance of life and growth of the organism, may, under certain conditions, exert a definite toxic effect in so far as to cause fever and other attendant symptoms of a fairly uniform character. His views were based at first on clinical observations and were later corroborated experimentally in his laboratory by his associates, principally by L. F. Meyer.[2] On the basis of both experimental and clinical evidence the following conclusions were formulated:

1. The normal food of infants contains what he designated as "pyretogenic" and "apyretogenic" elements.
2. The sugars and salts belong to the first group.
3. Casein and other proteins belong to the second group and never give rise to fever.
4. The fever produced by sugar and salts is due to the direct action of these substances, and not to their influence on the bacterial flora.
5. In perfect health, neither salt nor sugar, even when given in considerable excess of the normal requirement, produces any disturbance of the body temperature.
6. It is the function of the intestinal wall and of the liver to keep in check the toxic tendencies of salt and of sugar.

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1. Finkelstein, H.: Deutsch. med. Wchnschr., 1909, v, 190.
2. Meyer, L. F.: Deutsch. med. Wchnschr., 1909, v, 194.

Our observations apparently contradicted the conclusions of Finkelstein regarding casein, and hence it became important to make certain whether or not the fever in our patient was caused by some unknown accident or was actually due to the casein intake. The subsequent observations were planned with a view of furnishing evidence in support of or against the pyretogenic influence of casein. The bacteriological studies were continued, as it was hoped that through them also some information might be obtained that would enable us to determine whether the rise of the body temperature accompanying the high intake of casein was the result of a direct action of the protein or indirectly due to its influence on the intestinal flora.

The circumstances under which the rise of body temperature first occurred were the following: In order to secure a diet containing the maximum part of the calorific requirement in form of protein, milk had to be avoided as the solvent of the casein, as such a mixture generally gave too high a calorific value to the food. The casein was therefore dissolved with the addition of a solution of sodium hydrate; the final mixture being, however, rather on the acid than on the alkaline side. This preparation (for details on composition see Miss Courtney's paper) is referred to subsequently in this article as the "synthetic" food. It varied slightly in its percentages when prepared at different times; its average composition was, however, fat, 2 per cent.; sugar, 1.8 per cent.; protein, 6 per cent.

On the fourth day, while taking this food, the infant abruptly developed high fever, great restlessness and other symptoms of discomfort, which ceased as soon as the food was changed.

Careful and repeated physical examinations of the infant were made, but failed to reveal any pathologic condition of the internal organs to which the fever could be attributed. Hence, attention was again directed to the composition of the food during the "synthetic" period and during that of the high protein intake which immediately preceded it. The only important difference appeared to be a reduction in the amount of whey added. For six days this child had taken a milk formula containing 5.5 per cent. protein without showing the slightest disturbance. On the contrary, he was happy, comfortable and gaining in weight; but on the fourth day, on the "synthetic" diet, fever and its attendant symptoms were seen.

The same observation was repeated on this child two months later, with results which were practically identical. After the temperature had been normal for a long time and the child to all appearance well, he developed, on the sixth day after beginning the "synthetic" food, high fever, accompanied by the symptoms previously seen. All these, as before, disappeared immediately with the change in food.

Observations on another infant gave essentially the same result. In this patient the protein percentage in the milk formula was gradually raised in the course of thirteen days from 4 to 6 per cent. It was kept at the latter figure for six days. During all of this period of high protein feeding, lasting nineteen days, the child remained well and gained weight. The "synthetic" food formula was then substituted, and promptly on the fourth day thereafter the child responded with an attack of fever. Since the symptoms were not so severe in this patient, the food was not changed as soon as fever occurred. As rather marked constipation existed, castor oil and then calomel were administered to determine whether or not constipation might be a factor. But the temperature was not influenced by the catharsis. Finally, on the seventh day of the fever, the food was discontinued and a simple milk dilution substituted. Immediately the temperature fell to normal and remained there.

On a third infant two observations were made. In the first one the protein percentage in the milk formula was gradually raised from 4 to 6 per cent. during a period of ten days. It was kept at the latter figure for five days longer. During this time there was no fever or sign of disturbance and a slight gain in weight. On the fifth day, after a change was made to the "synthetic" food, fever and the usual symptoms developed, ceasing at once when the food was changed to a simple milk dilution.

In a second observation on this infant a milk formula containing 6 per cent. protein was continued for sixteen days without fever or abnormal symptoms; but fever developed on the fifth day after a change was made to the "synthetic" food, which contained the same percentage of protein.

From the standpoint of metabolism, the only striking thing accompanying the fever was the complete retention of the chlorids. This was seen in all the cases. It began two or three days before the rise in temperature occurred and continued into the febrile period. The nitrogen retention was good, and the proportion of ethereal sulphates in the urine did not differ strikingly from the values obtained in other periods.

ANALYSIS OF THE FACTORS THAT MIGHT HAVE BEEN INSTRUMENTAL IN CAUSING THE FEVER

That its occurrence was not accidental seems established by its regular development in every observation at approximately the same time after beginning the "synthetic" food; also by the fact that although these patients were under observation for several months, no similar attacks were seen under other conditions; nor was there evidence in any case that the fever was due to intercurrent illness as a complication.

This possibility was always borne in mind; the patients were frequently examined and watched for local symptoms of every sort. As already mentioned, in only one case was constipation marked, and in this patient free catharsis did not influence the fever. Furthermore, the stools in most of the observations, both before and during the fever, were quite normal.

The changes in the intestinal flora were very similar in all the observations. There was a very great reduction in the number of fermentative organisms (it will be remembered that in all the cases the percentage of carbohydrates in the food was low, usually 2 per cent. or less), and a great increase in the proteolytic varieties. That the fever was due to infection from the latter seems highly improbable for several reasons: The flora during the attack did not differ essentially from that which existed for several days before and several days after the fever; the symptoms developed very acutely, and if the food was at once changed they ceased almost immediately; furthermore, the stools gave no evidence of any such infective process.

The rise of temperature invariably occurred after the "synthetic" food had been given and on no other diet, and that it came regularly in each case after the food had been taken for about the same length of time, points strongly to the food as the cause of the temperature. What was it in the food, then, which brought about this result? Was it simply cumulative effect of previous high protein feeding, or was it something in the "synthetic" food mixture?

The first hypothesis seems disproved by two of the observations. Whereas, in the others the temperature occurred in about ten days after beginning the high protein feeding, in two instances very high protein (in one child, between 5 and 6 per cent. for eleven days, in the other 6 per cent. for sixteen days) had been given without producing fever or other abnormal symptoms. Yet in both fever developed on the fourth day after the change was made to the "synthetic" formula.

The "synthetic" food formula did not differ essentially in the percentage of fat, sugar and protein from the food which immediately preceded it and which produced no fever. On the contrary it was the aim to make the percentages in the two foods as nearly identical as possible. The only difference was in the mode of preparation. To the "synthetic" food to effect a solution of the casein in the minimum amount of whey, sodium hydrate was added. The daily amount used was about 1 gm. In spite of this addition the total salt intake of the infant while on the "synthetic" food differed but little from that taken in the period immediately preceding. Thus the average salt intake of Case 1 for ten days before the "synthetic" food was 12.2 gm.; during the four days of the "synthetic" period it was 10.9 gm. In Case 2 the intake in the ante-

cedent period averaged 6.9 gm.; during the "synthetic" period it averaged 7.1 gm. In Case 3 the average intake for eighteen days before the "synthetic" period was 9.03 gm.; for the five days of the "synthetic" period it averaged 9.50 gm.

It would appear, therefore, that the total salt intake could not be regarded as a factor in producing the fever. That the sodium hydrate added was of itself sufficient to cause a rise in temperature seemed most improbable. One observation was made, however, which bears on this point. Since sodium hydroxid was used to neutralize the phosphoric acid of the casein, sodium phosphate was added to a diet which had caused no fever (fat, 2 per cent.; sugar, 6.5 per cent.; protein, 2.6 per cent.); this was continued for four days without result so far as fever was concerned.

Inasmuch as the "synthetic" food was low in sugar (about 2 per cent.), although not lower than the food used in the period immediately preceding it, one observation was made on Case 3 during the febrile period to determine whether the addition of lactose to make the proportion in the food 5 per cent. would affect the fever. This was continued for two days without result. But two days later the fever ceased, twenty-four hours after the food had been changed.

We come now to a consideration of the amount of whey in the "synthetic" food formula as compared with that used in the other food formulas containing high protein. The latter were prepared (*vide* Miss Courtney's paper, Part IV) after the manner of Finkelstein's *Eiweissmilch*. In 1,500 c.c. of this food which were prepared for one day, there were used 600 c.c. of milk; while in the "synthetic" formula but 200 c.c. of milk. It will be remembered that no child took over 1,260 c.c. daily, and therefore the whey received was less than 175 c.c. It seems to us that the most probable explanation of the fever observed in these infants is the administration of the large amounts of protein without a sufficient amount of whey.

As to the actual significance of the retention of the chlorids, we have at present no definite information. It is, however, noteworthy that the chlorid intake in the "synthetic" food averaged about 0.50 gm., while that on the other foods was nearly three times as great; but such a reduction of the chlorids in normal infants did not bring about a complete disappearance of the chlorids from the urine.

CONCLUSIONS

1. Alimentary fever may under certain conditions occur in infants after administration of casein of cow's milk and perhaps of other proteins.

2. The rise of the body temperature was observed only when the food mixture was made up so as to contain about 6 per cent. of protein (chiefly casein) and a minimal quantity, only about 150 to 175 cc. of milk daily.

3. The rise of body temperature was invariably accompanied by a retention of chlorids, which, however, usually preceded the febrile attack by two or three days.

4. After the first rise of temperature the fever persisted so long as the diet was continued, but in every instance promptly disappeared as soon as the food was changed.

5. The fever is apparently due to the direct action of the absorbed protein, since the bacterial conditions of the intestines noted during the period of the "synthetic" food were not different from those noted during the preceding period. Also, Conclusion 4 speaks in support of this view.

6. From the observations here reported it would appear that the changes in the food influenced the chemistry of the excreta more than they did the bacteriology. For while the chemical changes resulting from the food variations differed considerably in the individual cases, the bacteriology changed along the same general lines in all. In view of this fact and of the slow changes in the intestinal flora noted in these observations, such changes would seem to have but a limited application for therapeutic purposes, though a very definite one when the food changes can be made sufficiently great.

7. It seems clear from these observations that one may use considerably higher percentages of protein in milk formulas than the 3.5 per cent. of Finkelstein's formula. This is a point which may be of much practical importance in conditions in which there is marked intolerance both of fats and carbohydrates. Such high proteins as 4.5 per cent. or over should only be used for limited periods, and never given at all except with a suitable proportion of whey.

8. This report emphasizes the physiologic importance of whey in the nutrition of infants and other young animals. While laying stress on the dangers of whey, especially from its sugar content, in many forms of intestinal disturbance, Finkelstein and Meyer have also appreciated the dangers to nutrition which may follow reduction of the salts. Recently Osborne and Mendel[3] also have found that the mineral salts in the proportion present in whey were absolutely essential for the growth of animals, and that in the absence of salts, though maintenance of life was possible, growth could not be induced. As yet it is not possible to

3. Osborne, T. B., and Mendel, L. B.: Carnegie Inst. of Washington, Pub. 156, 1911, i and ii.

formulate any definite opinion as to the nature of the whey components which inhibit that action of casein, which, in the absence of whey, causes the rise of body temperature.

9. The present observations call special attention to the work of V. C. Vaughan[4] and his collaborators, who have repeatedly reported the production of fever by the subcutaneous injection of various proteins. Whether or not the fever induced clinically in our cases and experimentally by Vaughan is occasioned by the same mechanism, remains to be established.

PART II.—CLINICAL OBSERVATIONS

ALAN BROWN, M.D.
Resident Physician to the Babies' Hospital
NEW YORK

CASE 1.—Francis H. was admitted as a case of marasmus July 11, 1911, aged 8 months, having suffered from digestive disturbances, chiefly intestinal, since 3 months of age. At the time of admission he weighed but 3,850 gm., had no acute symptoms, but was suffering from chronic otitis and was very backward in physical development. During the next two months his digestion and general condition slowly improved. There was an initial loss in weight of 350 gm. till July 24, when he touched his lowest point, 3,500 gm.; from this time there was a steady but slow increase in weight amounting to over 800 gm., and he was taking a formula made from whole milk, containing fat, 2.6 per cent.; sugar, 5 per cent.; protein, 2.4 per cent.; 180 c.c. for each of seven feedings. His stools for the most part were good; no acute symptoms were present.

Metabolism observations were begun on September 14, at which time his weight was 4,330 gm. His appetite was excellent, there was no vomiting and his stools were 3 to 4 daily, usually yellow in color and seldom contained mucus. No change in food was made for two weeks. He continued to gain in weight, his stools were for the most part yellow and smooth, but at times became thin and loose. The number greatly increased while in the metabolism bed; there were eight to eleven daily, but most of them were small. The temperature remained normal and the child was comfortable and happy.

On October 1 the food was changed to a formula consisting of fat, 2.6 per cent.; sugar, 3.0 per cent.; protein, 2.4 per cent. The reduction in sugar was made on account of the rather frequent, thin stools. This food was continued for three weeks. The stools were less frequent but still somewhat thinner than normal and yellow, averaging from seven to nine daily. The child was kept in the metabolism bed, except for an interval of two days, the weight up to this time being about stationary.

October 14 the food was changed to fat, 0. per cent.; sugar, 6 per cent.; protein, 3.5 per cent. This was fat-free cow's milk with the addition of 1.5 per cent. cane sugar. This food was continued for five days, during which time he gained 250 gm. in weight and seemed perfectly comfortable. The stools showed, however, a marked and immediate change; they became large, loose and contained quantities of greenish-brown jelly-like mucus; there were from eleven to thirteen daily.

October 19 the food was made fat, 1.6 per cent.; sugar, 4.7 per cent.; protein, 3 per cent. This formula was obtained from partially skimmed milk with the

4. Vaughan, V. C., Cumming, J. G., and Wright, J. H.: Ztschr. f. Immunitätsforsch., 1911, ix, 458; Vaughan, Cumming, and McGlumphy, C. B.: ibid., 1911, ix, 16.

addition of .75 per cent. of cane sugar. This was continued for five days. With this change the amount of mucus somewhat diminished, the stools were reduced to eight a day and they were not so thin. The child lost during the five days about 100 gm. in weight.

October 25 he was given casein milk (*Eiweissmilch*), three parts, and barley-water, one part, the formula being fat, 1.9 per cent.; sugar, 2.3 per cent.; protein, 2.9 per cent. The effect of the reduction in the sugar was immediate and very striking. The stools became smooth, soft, brown, formed, from three to four a day, and the amount of water in the stools which had been from 100 to 300 c.c. daily was reduced to 36 to 43 c.c. a day.

October 31 his food was changed to a formula consisting of fat, 3.6 per cent.; sugar, 3.1 per cent.; protein, 5.6 per cent. This was continued for one week; during this time the stools were gray, yellow, dry and formed, from four to five daily. He more than regained his lost weight, having reached 4,980 gm. His first metabolism period closed November 6.

During the interval between November 6 and 16 he was out of the metabolism bed and was being fed casein milk of the following percentages: fat, 2.75; sugar, 1.8; protein, 3.9 The weight remained stationary and the stools averaged three to four a day, being yellow, pasty and at times formed.

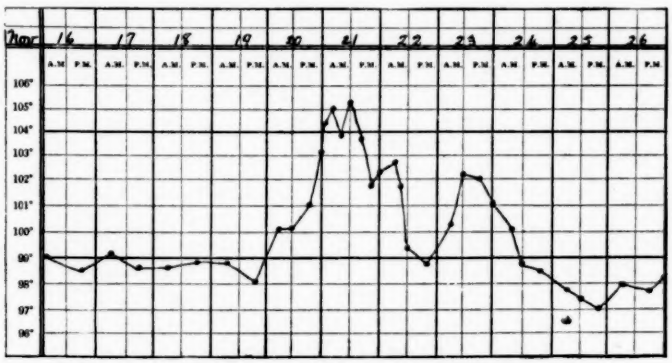

Chart 1.—Temperature of F. H.; first attack of fever.

November 16 he was again put in the metabolism bed and the food was changed to the following: fat, 2.9 per cent.; sugar, 1.5 per cent.; protein, 5.8 per cent.; this is referred to in the chemical report as the "synthetic" food. Up to this time the general condition of the patient was excellent; he was happy, comfortable and did not appear to be disturbed by the restraint of the metabolism bed. For the first four days he took his food well. The character of the stools, on this new food, changed considerably. They became gray, formed, dry and crumbly, occasionally being coated with mucus. The frequency remained about the same, three to four daily. On the nineteenth he refused 120 c.c. of the 1,260 c.c. offered, but showed no other signs of disturbance. On the morning of the twentieth the temperature was 100.2 F.; he vomited once and took less than half of his usual food. He was restless, fretful, irritable, and had a slight cough and a few coarse râles in the chest. His slight bronchitis was thought sufficient to explain his symptoms. The course of his temperature is shown on the accompanying chart (Chart 1). In the early morning of the twenty-first it was 105.2 F.; the child was pale, considerably prostrated, breathing rapidly, restless and continually rolling his head from side to side. His symptoms suggested the beginning of a pneumonia, although the only signs in the chest were a few râles. The suspicion was strengthened on examination of the blood which showed a leukocytosis of 27,160. Further evidence was shown by examination of the urine which showed a total absence of chlorids.

He was immediately removed from the metabolism bed, given castor oil, the colon was irrigated and the child put on a food consisting of 1 part of whole milk and 3 parts water, with lactose added; formula; fat, 1 per cent.; sugar, 5 per cent.; protein, .9 per cent. Under this régime he rapidly improved and in two days was apparently as well as ever. During this period, November 16 to 21, he lost in weight 447 gm. The next blood examination made November 25 showed the leukocytes to be 9,200.

Between November 23 and December 11 he was fed on dilutions of whole milk, till on December 8 he was taking a food consisting of fat, 3 per cent.; sugar, 4.5 per cent.; protein, 2.6, with the addition of 24 c.c. of maltose and 6 c.c. of olive oil daily. His stools averaged two to three a day, were generally yellow and smooth.

He was again put up in the metabolism bed on December 12, the food being fat, 2 per cent.; sugar, 6.4 per cent., protein, 2.5 per cent. Of the sugar, 1.25 per cent. was maltose, also mono- and di-sodium phosphate were added. This was continued for four days without any effect on the temperature or on his other symptoms so far as could be determined. He was removed from metabolism bed December 23, having gained about 120 gm. during the period.

Chart 2.—Temperature of F. H.; second attack of fever.

December 26, after an interval of three days he was again put in the metabolism bed and given the "synthetic" food containing fat, 2.1 per cent.; sugar, 1.7 per cent.; protein, 6.3 per cent., 1,260 c.c. daily. A blood-examination made two days later showed a leukocytosis of 24,400, but this was possibly explained, in part at least, by a slight otitis. After the first day he took his new food well and his weight remained nearly constant. The stools were from four to five a day, light gray and formed, with occasionally a slight amount of mucus. He was comfortable, quiet and exhibited no nervous symptoms.

December 31, he refused nearly all of his food and he seemed somewhat out of sorts; in the evening a sharp rise of temperature occurred to 103.8 F. and a repetition of practically all of the symptoms noticed in his previous disturbance on a similar food November 21.

A dose of castor oil, and an immediate change of food to diluted whole milk were followed by a prompt fall in temperature and a speedy disappearance of all his symptoms. A temporary drop in weight of nearly 700 gm. occurred during this upset, but this was quickly regained and for the next five days his appetite was good, his stools normal, and his general condition excellent.

On January 25 he was discharged from the hospital in good condition. His progress after the last observation was without event and no disturbance of digestion occurred. His daily weights during the period of observation are given in Chart 3.

CASE 2.—Jacob S. was admitted Dec. 11, 1911, aged 5 months; suffering from malnutrition; weight 3,437 gm. The patient had gained little since birth, his digestive symptoms being chronic constipation and frequent vomiting. For the first two and one-half months in the hospital he was fed chiefly on dilutions of whole milk, with small amounts of maltose added. His digestive symptoms steadily improved. His stools averaged two to three a day, usually smooth and pasty, and he gained 551 gm. in weight.

February 27 he was put up in the metabolism bed and given a milk mixture whose formula was fat, 1.45 per cent.; sugar, 5 per cent.; protein, 3.5 per cent. He was given 150 c.c. for each of seven feedings, with 15 c.c. of olive oil every day. Two days later the protein percentage was increased and the sugar decreased, the formula being: fat, 1.45 per cent.; sugar, 4.5 per cent.; protein, 4.0 per cent. The percentage of protein was gradually raised and that of the sugar lowered at three day intervals until on March 13 he was taking fat, 1.45 per cent.; sugar, 2.1 per cent.; protein, 6 per cent., made after the manner of casein milk. On March 11 the olive oil was reduced to 6 c.c. and 5 per cent. lime water was added on account of occasional vomiting.

March 18 the food was changed to the "synthetic" food: fat, 1.45 per cent.; sugar, 1.8 per cent.; protein, 6 per cent. Up to this point he had done extremely well; had gained 501 gm. in weight and averaged three to four stools daily, which were for the most part yellow, pasty, but small, and inclined to constipation. He

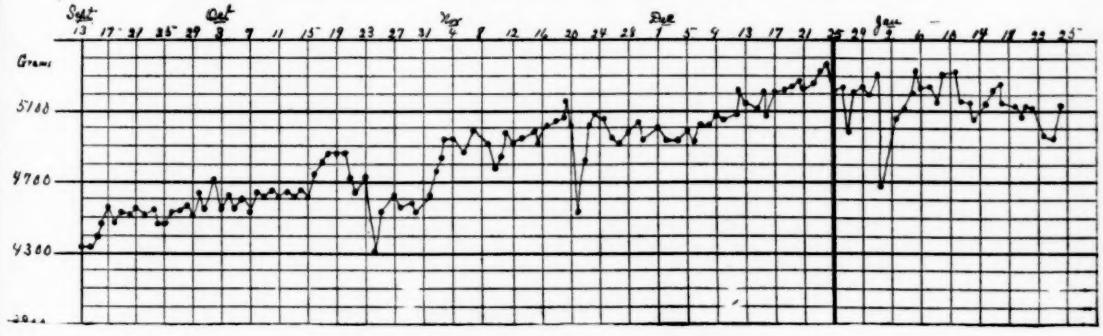

Chart 3.—Daily weight chart of F. H.

manifested no unusual symptoms and appeared in every way normal. After taking this food well for three days he showed his first sign of disturbance, which was to refuse some of his food. At noon of the following day (twenty-first) the temperature rose to 99.4 F.; at 7 p. m. it was 103.2 F.; it fluctuated irregularly for the next week, usually being between 100 and 102 F. During this period (up to March 27) his food was unchanged but he took it badly, frequently leaving more than one-half of the amount offered. The stools averaged three to six a day; they were small, of a yellow-brown color, often dry, hard balls, quite different from those of Case 1 on the same food.

It was thought that his constipation might be the explanation of his temperature. He was given two drachms of castor oil, and later calomel. The stools following catharsis were loose and contained considerable mucus, but the temperature continued. Careful and repeated physical examinations revealed no local cause for his temperature. He had few symptoms except a moderate amount of irritability, marked anorexia and a rapid loss in weight.

Beginning March 25, 30 c.c. breast milk were given before each feeding. This produced no change in the symptoms and finally on March 27 the "synthetic" food was stopped; whereupon the temperature rapidly fell to normal and remained so, except for one slight rise several days later, due to antitoxin. He rapidly regained his appetite and in three or four days was gaining steadily in weight.

The blood-examinations made are given in a subsequent table.

The patient was discharged from the hospital six weeks later in good general condition, weighing 4,471 gm.

For daily weight record during the period of observation see Chart 5.

CASE 3.—F. D. was admitted September 14, 1911, aged 4 months, suffering from chronic indigestion, weight 3,045 gm. From this date, except for one slight upset in December, his digestion and general condition improved; he took his food

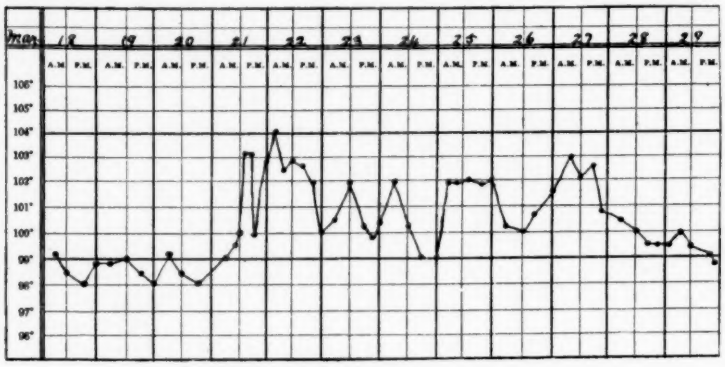

Chart 4.—Temperature of J. S.

well, vomited but seldom, and his stools averaged three to four a day, were brown, pasty, at times somewhat constipated. His feedings consisted for the most part of dilutions of whole milk; his best weight, in December, showed a gain of 1,230 gm.

January 5 he was put in the metabolism bed and given a food consisting of fat, 1.5 per cent.; sugar, 2.2 per cent.; protein, 3.4 per cent. The protein was

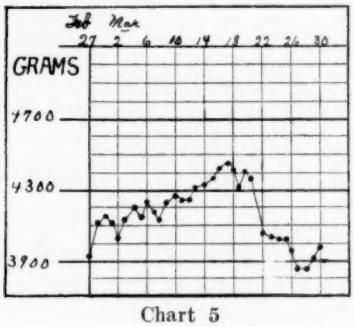

Chart 5

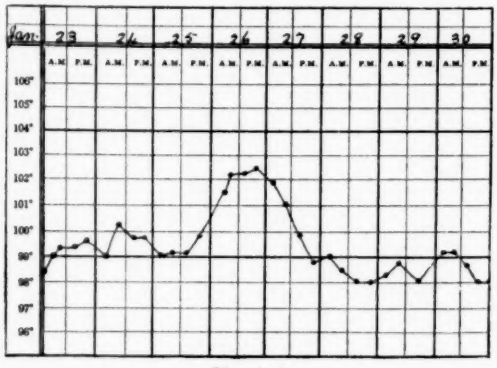

Chart 6

Chart 5.—Daily weight chart of J. S.
Chart 6.—Temperature of F. D.; first attack of fever.

gradually increased at three day intervals to 6 per cent. on January 18. He gained 164 gm., was happy and comfortable and his stools averaged six to seven a day, usually gray and pasty, rarely loose.

January 22, he was given the "synthetic" food: fat, 1.8 per cent.; sugar, 1.8 per cent.; protein, 5.9 per cent. On the evening of January 25 his temperature rose to 99.8 F. and in the morning of the following day to 101.6 F. The fever

was accompanied by irritability, restlessness, rapid breathing, and considerable prostration. He was immediately removed from the metabolism bed, given a cathartic and the food changed to a formula made from whole milk containing of fat, 1.5 per cent.; sugar, 5 per cent.; protein, 1.4 per cent. These measures were followed by an almost immediate change for the better. The loss in weight of 180 gm. was quickly regained and he continued to improve till his discharge on March 5, when his general condition was exceilent.

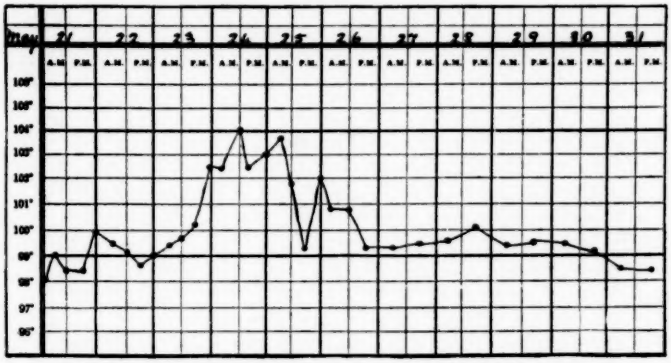

Chart 7.—Temperature of F. D.; second attack of fever.

March 19 the patient was readmitted with symptoms similar to those with which he first entered the hospital. For the following six weeks his digestion and general condition improved and he gained 720 gm. For the most part his food consisted of various dilutions of whole milk with sugar added and his stools were good.

On May 1 he was put in the metabolism bed, his food being: 2.6 per cent. fat, 4.5 per cent. sugar, 5 per cent. protein, and in addition was given 7.5 c.c. of olive oil each day. The protein in his milk was increased to 6 per cent. on May 4 and then kept at this point. During the interval between May 1 and 20 he gained 350 gm. His stools averaged two to three a day, mostly yellow and pasty, at times dry and constipated, requiring an occasional dose of magnesia. In his general condition he improved steadily.

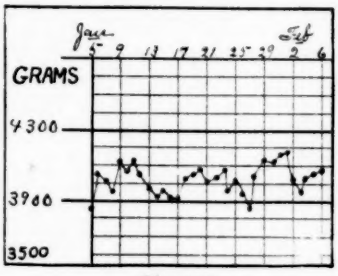

Chart 8

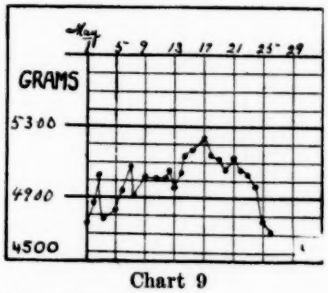

Chart 9

Charts 8 and 9.—Daily weight charts of F. D.

On May 20 he was put on the "synthetic" food; except for the existence of constipation nothing noteworthy happened until the evening of May 23 when the temperature rose to 101.8 F., but no other manifestations occurred till the afternoon of May 24, when he was noticed to be restless, refused part of his food and vomited once. On May 24 lactose to 5 per cent. was added to the "synthetic" formula but with no apparent effect on the symptoms. On the morning of May

25 the symptoms practically identical with those observed on previous similar occasions with other children developed, but of greater severity. He was immediately removed from the metabolism bed, given a cathartic and the food changed to a dilution of whole milk. With these measures all the symptoms speedily disappeared and in thirty-six hours he was apparently as well as ever.

He was discharged June 27 in good general condition, having gained 1,740 gm. since March 20.

In Table 1 are given the results of the various blood-examinations made in the different cases.

TABLE 1.—RESULTS OF BLOOD-EXAMINATIONS IN THE THREE CASES

Case	Period	Condition	Total Number Leukocytes	Polymorphonuclears, Per cent.	Lymphocytes, Per cent.	Remarks
F. H.	Nov 21..	First day of fever	27,160	57.6	37.0	.....
	Nov. 25..	First day of normal T.	9,240	37.3	54.0	.....
	Dec. 30..	Normal temperature	20,200	46.0	49.0	Slight otitis present
	Dec. 31..	Fever beginning	17,900	42.0	52.0	.....
	Jan. 1..	Fever high	17,400	49.5	41.5	.....
	Jan. 2..	No fever	18,200	46.0	45.3	.....
	Jan. 3..	No fever	14,200	39.2	49.5	.....
	Jan. 4..	No fever	13,800	43.0	47.0	.....
	Jan. 5 to 8.	No fever	16,400	47.3	46.9	Average for four days
J. S.	March 13..	No fever	18,400	42.0	51.5	.....
	March 16..	No fever	18,800	51.0	49.0	.....
	March 20..	No fever	19,800	....	....	.....
	March 21..	Fever began	.....	....	....	.....
	March 23..	Fever present	14,400	57.0	43.0	.....
	March 24..	Fever present	16,400	42.0	57.0	.....
F. D.	Jan. 22-25..	No fever	8,700	....	....	Average for four days
	Jan. 26..	Fever began	10,700	....	....	.....
	Jan. 27..	Fever present	14,300	....	....	.....
	Jan. 28..	No fever	10,000	....	....	.....
	Jan. 29..	No fever	8,300	....	....	.....
	May 21-23..	No fever	15,600	54.3	42.0	Average for three days
	May 24..	Fever high	20,000	50.0	50.0	.....
	May 25..	Fever high	20,000	46.0	54.0	.....
	May 26..	Fever slight	18,200	44.6	55.0	.....
	May 27..	No fever	12,800	42.0	58.0	.....
	May 29..	No fever	9,200	47.3	52.6	.....

Case 1 in the first period with high temperature showed marked polymorphonuclear leukocytosis,[5] which quickly disappeared when the temperature became normal. In the second period the variations during the fever from the average for the child were so slight as to be without significance.

5. It is to be borne in mind that in infants of this age and type the lymphocytes normally exceed in number the polymorphonuclear cells.

Case 2 showed no marked variations during the febrile period from the findings before and subsequent to it.

Case 3 showed a distinct leukocytosis coming with the fever and disappearing with it. In the second observation on this patient the same thing was seen, the differential count being inconclusive.

SUMMARY

In every one of the five observations made on the three infants, an attack of fever followed the administration of the "synthetic" food, although in all the temperature had been previously normal for a considerable period. Three times this developed on the fourth day, once on the fifth and once on the sixth day. In four observations the patients had previously taken as high, or nearly as high, a percentage of protein in food prepared differently for much longer periods (in one case for sixteen days) without the development of fever. In every instance the fever developed abruptly without other warning than anorexia and some restlessness which usually preceded the rise of temperature for about twelve hours. The fever persisted so long as the diet was continued, but ceased almost at once when the food was changed to a simple milk dilution. With the fall in temperature all of the general symptoms speedily disappeared.

The highest temperature noted was 105.4 F. In the patient showing the least reaction it rose to 102.5 F. The average rise was to 104 F. Marked nervous symptoms usually accompanied the fever; constant rolling of the head, extreme restlessness, pallor, rapid respiration, considerable prostration, and in three observations marked leukocytosis. In one case the white cell count reached 27,000. Digestive symptoms, except anorexia, were conspicuously absent. Initial vomiting was noted but once; the bowels were usually somewhat constipated but not otherwise abnormal; a moderate abdominal distention was noted but once; neither pain nor tenderness was evident in any case. The urine showed several times an increased indican reaction, but this was not constant nor persistent. Pallor, rapid respiration and prostration were marked in all but one case. In every instance there was rapid loss of weight, which was due partly to the refusal of food and partly to catharsis. This loss was soon repaired in nearly every case. In none of the observations did the symptoms resemble an ordinary attack of acute indigestion.

PART III.—BACTERIOLOGIC OBSERVATIONS

MARTHA WOLLSTEIN, M.D.
Pathologist to the Babies' Hospital
NEW YORK

Throughout these five periods of observation the method of procedure was the same. Specimens of feces obtained from the rectum were studied bacteriologically for several days before the chemical examination

of the excreta was begun. This served the purpose of establishing a control for each child. Throughout each period of study daily examinations of the feces were made.

TECHNIC

The samples of feces were obtained in the usual way, by introducing into the rectum a glass tube of narrow caliber, plugged at one end and sterilized. As a rule, the tube became filled with fecal matter within a few seconds, but during the periods of constipation it was difficult to obtain more than a small amount, sometimes less than half a cubic centimeter, in several minutes. Occasionally no material at all could be obtained even in more than one attempt. From the fecal specimens smears were prepared and stained by Gram's method, the remainder of the material being at once emulsified in neutral, dextrose-free broth. The emulsion was made as thorough as possible, and care was taken lest it be too thick. This emulsion served to inoculate glucose and lactose fermentation tubes, whole milk tubes and tubes of the acid-dextrose-broth introduced by Heymann, and described by Finkelstein[6] as consisting of 2 per cent. dextrose in 0.5 to 1 per cent. acetic acid broth. Agar and gelatin plates were also poured from the tube of emulsified feces, which was then itself incubated and compared with the growths in the acid broth on the following day. The cultures were incubated both aerobically and anaerobically, but it was soon found that anaerobic cultivation of plates poured directly from the fecal emulsion was utterly useless, since the colon varieties overgrew all other forms. Anaerobic incubation was, therefore, reserved for the cultivation of second or later generations from the acid broth or fermentation tubes, and of colonies isolated from deep agar sticks and grown further on plates or in fluid media.

It may be said at the outset that the varieties of bacteria isolated from the stools of these three infants were not numerous. There was a marked sameness noted in the bacteriology throughout all the observations, a fact which was to be expected since the food was practically the same in the parallel stages of the five observations. While by no means every variety of bacterium seen in smears and cultures from the feces was isolated in pure growth, the great majority were certainly so obtained. The most useful media proved to be the lactose broth in the fermentation tubes, and the acid-dextrose broth or Heymann's medium. Gelatin plates were useful in giving a general idea of the varieties of liquefying organisms present. Whole milk tubes proved to be disappointing as indicators of the presence of proteolytic bacilli, for the reason that streptococci which peptonized milk were very numerous in the

6. Finkelstein, Deutsch. med. Wchnschr., 1900, xxvi, 263.

feces of these children, and it was repeatedly noted that on a diet rich in carbohydrates, where the cultures showed the presence of a fermentative and not a proteolytic flora, the amount of gas in the fermentation tubes was comparatively low as was to be expected, but the milk tubes were more than 80 per cent. peptonized. As a control a breast-fed baby was studied. This child showed the typical bifidus picture in smears and cultures from the stool. Only 0.5 to 1 c.c. of gas was formed in the lactose fermentation tube, and yet the milk tubes were almost completely peptonized. The liquefying streptococcus was found in large numbers in the stool from this infant.

BACTERIOLOGY OF THE FOOD

In order to determine whether the bacteriologic intake with the food bore any relationship to the fecal flora, samples of the food were studied at intervals. At the beginning of the first observation, Sept. 13, 1911, the prepared food contained *Streptococcus, Albococcus, B. lactis aerogenes* and a liquefying, fluorescent bacillus. There were 12,000 colonies to 1 cubic centimeter of food. Nine days later the number of colonies had risen to 3,500,000 per c.c., and *B. subtilis* was isolated as well as the other varieties. It became obvious that a cleaner milk was needed, and a change was made on October 11. The number of colonies in the new milk used numbered only 1,600 to the cubic centimeter, and were composed only of staphylococci and streptococci. The food after it had been prepared for the feeding of the child, however, contained 16,000 to 19,000 colonies to the cubic centimeter, and on several successive days *Streptococcus, Aurococcus, Albococcus* and *B. coli communior* were found. Greater cleanliness in handling of the bottles was then instituted, and after November 1 no further contaminations appeared in the food. The protein milk contained the largest numbers of bacteria, 200,000 to the cubic centimeter being present on one occasion. This was reduced to 30,000 later. From the ripened milk used in preparing the protein milk a long gram-positive bacillus was isolated. It grew very faintly on agar, fermented lactose, and coagulated milk softly without peptonizing the curd to any extent. This bacillus was looked on as *B. Bulgaricus*, described as a powerful lactic acid ferment by Cohendy,[7] and with which the milk was said to be ripened. Herter and Kendall[8] found this bacillus in the feces of a rhesus monkey fed on *bacillac*.

The "synthetic" food never contained over 2,000 colonies to the cubic centimeter.

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7. Cohendy, M.: Compt. rend. Soc. de biol., 1906, lx, 558.
8. Herter and Kendall: Jour. Biol. Chem., 1908-9, v, 293.

Five observations were made on three children. The details of the bacteriologic findings during the course of the studies follow:

Observation 1.—F. H., 9½ months old. Sept. 13, 1911. Food, modified milk having percentages of fat, 2.6; sugar, 5; protein, 2.4; containing albococci, streptococci, fluorescent bacilli which liquefy gelatin, and *B. lactis aerogenes.*

Feces yellow, no mucus present. The material was granular and did not make a smooth emulsion in dextrose-free broth. Smear shows oval cocci in pairs and chains, slender, gram-positive bacilli, some with pointed, tapering ends (acidophilus); granular or vacuolated bacilli, some with poles staining deeply; gram-negative bacilli like *B. coli* forming a background for the larger, blue, bacillary forms. No spores were seen.

From agar plates an oval streptococcus, the *Enterococcus*, and *B. coli communis* were isolated. In the fermentation tubes small numbers of *B. bifidus* grew, and were subcultured, though not isolated, in acid broth in the anaerobic jar (pyrogallic acid—hydrogen—vacuum method). *B. acidophilus* was isolated from the acid broth tube. Only 1.5 c.c. of gas formed in the fermentation tubes of lactose broth, and 1.25 c.c. in the glucose broth. Milk was coagulated and slightly peptonized.

September 16.—Three days later there were more blue than red bacteria noted in the gram-stained smear, and in the cultures *staphylococci, streptococci, B. acidophilus, B. bifidus, B. coli communis,* and *B. fluorescens* liquefying gelatin were noted. Only 1 to 1.5 c.c. of gas formed in the fermentation tubes, and whole milk was markedly peptonized, only a small solid coagulum remaining in the bottom of the tube. On gelatin plates liquefying green colonies and liquefying white colonies developed of fluorescent bacilli and albococci.

This picture varied but slightly during the following week, *B. coli communis* being found one day and a strain of the Shiga (non-mannite fermenting) type of *B. dysenteriae* another day. The history disclosed the fact that the child had suffered from "loose bowels" for a period of four weeks before admission, which was sought because of vomiting, diarrhea and colic.

September 23 *B. subtilis* was found in the feces. The colon bacilli were very numerous, but *B. bifidus* was present in comparatively smaller numbers. These relative proportions continued until the change to cleaner milk October 11, four days after which date no more subtilis bacilli were noted.

October 15: Food, milk with percentages, fat, 0; sugar, 6; protein, 3.50.

October 16. Cocci and colon bacilli were very numerous; *B. acidophilus* was present and *B. bifidus* had increased in numbers. *B. lactis aerogenes* was also found. The amount of gas produced was small and milk was coagulated but only very slightly peptonized.

October 19. Food changed to fat, 1.6; sugar, 4.5; protein, 3.

The numbers of *B. coli* were very numerous, *B. communior* being found on several successive days. Staphylococci, diplococci and streptococci were present in very large numbers.

October 20. *B. perfringens* (*B. aerogenes capsulatus,* Welch) was noted.

October 23. A fluorescent, liquefying bacillus was found on gelatin plates.

October 24. Food changed to protein milk, diluted with barley water: fat, 1.9; sugar, 2.3; protein, 2.9, but the child refused it for twenty-four hours.

October 25. A specimen was obtained after the child had fasted one whole day. The smear showed an equal number of gram-negative and gram-positive bacteria, having hitherto always shown more of the Gram-positive type. The change was due to the small numbers of cocci present, while colon-like bacilli were numerous and some gram-positive bacilli, apparently *B. aerogenes capsulatus,* were seen. The amount of gas in the fermentation tubes was more than twice as great as it had ever been, and in them *B. aerogenes capsulatus* was growing together with colon bacilli and cocci.

October 26. A long gram-positive bacillus was present in addition to the other varieties. This bacillus was apparently identical with the *B. bulgaricus* in the food, which was made up with ripened milk.

The only change noted in the next few days was a marked increase in the amount of gas found in the fermentation tubes, no new varieties of bacteria being noted.

October 31. Food changed to fat, 3.6; sugar, 3.1; protein, 5.5.

The amount of gas grew larger, the cocci decreased in numbers while colon bacilli and gas bacilli were numerous. There were very few bifidus forms seen.

November 6. Food of the same formula, but three drachms of maltose were added to relieve the constipation. From the dry maltose a large, gram-positive spore-bearing bacillus identified as *B. megatherium* was isolated. The day following the addition of the maltose to the food this spore-bearing bacillus was present in the feces. Castor-oil was given.

November 8. Cocci were very numerous; many colon bacilli and large spore-bearing, gram-positive bacilli were also seen. The spores in some of these bacilli were oval in shape, situated in the center of the organism, giving the whole bacillus an oval form; while in others a round spore lay at one end, giving the bacillus a nail-shape; in still others the spore was situated in the center of the bacillus and was narrower than the body of the rod, thus not changing its shape. Two forms of spore-bearing bacilli were isolated and identified as *B. mesentericus* and *B. megatherium*. Both peptonized milk without forming acid, both fermented dextrose and saccharose, *B. mesentericus* fermenting mannite as well. *B. bulgaricus* was still present.

November 10. The food was changed to fat, 3.1; sugar, 3.4; protein, 3.9, with the addition of four drachms of maltose.

November 12. The feces were alkaline to litmus paper. The suspension of feces in dextrose-free broth incubated twenty-four hours gave a very deep indol reaction. Milk tubes were coagulated and almost completely peptonized. Much gas formed in the fermentation tubes. Cocci were numerous, as were colon bacilli and *B. mesentericus* with many oval spores. *B. bulgaricus* was not found, though ripened milk was still used in the food.

November 16. The food was changed to the "synthetic" mixture, fat, 2.9; sugar, 1.5; protein, 5.8.

November 18. Cocci and colon bacilli were numerous. The feces were alkaline to litmus and a twenty-four hour culture in dextrose-free broth gave a deep indol reaction. The most numerous variety of organism present was a gram-positive bacillus isolated as *B. mesentericus*. On gelatin plates many slowly liquefying colonies developed.

November 20. In the smears there were many spore-bearing gram-positive bacilli on a background of colon-like gram-negative bacilli; some cocci; some gram-positive bacilli without spores. In the fermentation tubes the gas was reduced to half the quantity of the previous days, and in the one containing lactose broth some acidophilus and very many bifidus bacilli grew together with *B. mesentericus* and cocci.

November 21. After a sharp rise in temperature and the development of some prostration, a laxative was given and the food changed to barley water for a day. The laxative brought away large numbers of the organisms present the day before, and more *B. acidophilus* and *B. bifidus*, and, in addition, *B. aerogenes capsulatus*.

During the next week the child was fed only diluted milk, varying from fat, 1.2; sugar, 5; protein, 1, to fat, 2.20; sugar, 5; protein, 1.75. The spore-bearing bacilli diminished in number but did not disappear entirely. *B. bifidus* remained in small numbers, and so did *B. aerogenes capsulatus*. Within another week, during which time the sugar in the food was kept at 4.50 per cent., *B. acidophilus* and *B. bifidus* had increased in number, and only an occasional spore-bearing bacillus was seen. The amount of gas diminished, and the milk-tubes were about half peptonized. The second observation was then begun on the same child.

Observation 2.—F. H., now 1 year old, Dec. 12, 1912. Food: Fat, 2; sugar, 5.7; protein, 2.6. Maltose in food. The cocci and the colon bacilli were numerous, but *B. acidophilus* and *B. aerogenes capsulatus* were more so. *B. megatherium* appeared in forty-eight hours (from the maltose). The amount of gas varied, but was rather large, and milk was almost completely peptonized.

December 26. "Synthetic" food begun: fat, 2.1; sugar, 1.7; protein, 6.3. During the next four days *B. mesentericus* appeared in large numbers, while *B. aerogenes* disappeared. The gelatin plates were rapidly liquefied. *B. acidophilus* was less numerous, *B. coli* more so.

December 30. Fever and prostration developed. Castor-oil was given, after which *B. bifidus* reappeared and increased markedly during the next four days, the food in that time being the milk formulas 1-5-.90 and 2.60-5-2.40.

Jan. 4, 1912. Cocci, colon bacilli, *B. acidophilus*, *B. bifidus*, and an ocasional *B. mesentericus*.

It will be noted that the changes in the intestinal flora throughout these two observations was a very gradual one, consisting of a diminution but not a complete disappearance of the normal fermentative flora and its replacement by some proteolytic varieties. While the relative differences in the proportions of the amount of protein and carbohydrates in the food were as wide as it is possible to make them in the feeding of an infant of this age, it nevertheless follows that as long as the diet remains one composed entirely of milk elements, the absolute proportions cannot be changed to such a degree as to alter the flora completely. Thus the slow and incomplete change is accounted for. Compared with the results of the experiments of Herter and Kendall[8] on kittens and monkeys, where the protein diet of meat and eggs was changed to one of milk plus dextrose, the difference is certainly a striking one. The presence of *B. acidophilus* at a time when the reaction of the feces was neither amphoteric nor alkaline to litmus, may be accounted for by the fact that this acid-loving bacillus really grows better in a slightly alkaline medium, a fact pointed out by Rodella.[9] Certainly *B. bifidus* branches very much more in acid than it does in alkaline media, which accounts for the straight forms seen in the stained smears from these stools, and proved to be *B. bifidus* by culture in the fermentation tubes containing sugar broth. It will also be observed that after the catharsis and a return to a diluted milk formula at the end of the periods of study, the child's intestinal flora was about the same as it had been at the beginning. The return to normal was practically accomplished in from seven to ten days.

Observation 3.—F. D., aged 4 months, Jan. 1, 1912. Food, milk with following percentages: fat, 2.40; sugar, .50; protein, 2.20. Gram-stained preparations showed the presence of cocci in pairs and chains, few colon-like bacilli and *B. acidophilus*. In cultures all these and *B. bifidus* appeared. Two days later *B. megatherium*, from the maltose used in the food, appeared in the feces. After a change to food made with ripened milk (1.7-2.20-3.5) *B. bulgaricus* was seen.

9. Rodella, A.: Centralbl. f. Bakteriol., 1901, xxix, 717.

With an increase of the protein in the food to 4.7 per cent. spore-bearing *B. mesentericus* appeared and the colon bacilli were numerous. *B. bifidus* was present in small numbers only. Gas production in the fermentation tubes was very marked, milk-tubes were peptonized and many liquefying colonies grew on gelatin plates. The "synthetic" food (2-1.50-6) was begun on January 22, and on the following day the colon forms were very numerous, but spore-bearing bacilli, together with acidophilus and bifidus gave the smear a gram-positive appearance. The spores were of a variety of shapes. Some were oval with only a small cap of bacillus body left at either end; some were round and placed at one end of the bacillus, giving an appearance similar to that of the tetanus bacillus, and some were of the same diameter as the bacillus body, in which they lay nearer one end than the other. Still both acidophilus and bifidus continued to grow until the rise of temperature and accompanying prostration on January 26. Many of the bifidus bacilli were vacuolated, and the *B. mesentericus* showed many gram-negative, evidently degenerated elements. On February 2 the picture was practically as it had been at the beginning of the study, but a few oval spore-bearing bacilli still remained. There was in general very little difference between this observation and the preceding ones.

Observation 4.—J. S., aged 7½ months. Food, milk with following percentage: fat, 1.45, sugar, 5; protein, 3.50. Feb. 27, 1912.

The preliminary examination of this child's rectal contents showed the presence of cocci in pairs and chains, comparatively few colon bacilli, some acidophilus and straight forms of bifidus, and very few spore-bearing bacilli probably taken in with the maltose added to the food. The picture was distinctly a gram-positive one. On the above food only a small amount of gas formed in the fermentation tubes, except on one day when, for no apparent reason, the gas formation was more than doubled and the comparative numbers of colon bacilli were greatly increased. Evidently peristalsis had brought down those bacilli from the region of the ileocecal valve just before the specimen was obtained for that day's observation. *B. bulgaricus* in small numbers appeared in the feces, but the cocci were by far the most numerous forms in both smears and cultures.

There was no appreciable change in the bacteria until the protein in the food reached 6 per cent. with 2.5 per cent. of sugar, when spore-bearing, gram-positive bacilli began to appear and *B. bulgaricus* was no longer found.

On this high protein food the floral changes proceeded slowly, cocci still remaining very numerous, colon bacilli gradually increasing in numbers, spore-bearing gram-positive bacilli increasing very slowly, and a few vacuolated forms of *B. bifidus* persisting.

March 18 the "synthetic food" began, fat, 2.1; sugar, 1.7; protein, 6.3, after which, although there were many free spores as well as those contained in both gram-positive and gram-negative bacilli, the numbers of acidophilus and bifidus bacilli were still so numerous as to grow without difficulty in lactose broth fermentation tubes and from them in deep stick lactose agar. After the febrile attack and the subsequent catharsis human milk was added to the infant's food. Within two days *B. bifidus* had appreciably increased in numbers, although *B. mesentericus* and spores were still present. On the third day *B. acidophilus* was isolated from the rectal contents. The return to a normal intestinal flora was more rapid in this child than in the other two. Whether the comparatively small amount of human milk (11 ounces) given him helped this event, or whether it was only a coincidence in a rather resistant baby, it is difficult to say without a repetition of the observation. It is suggestive, however, and agrees with Moro's[10] experience, that when human milk is given to an artificially-fed baby, the physiologic flora appears in the stools on the second or third day.

10. Moro, E.: Jahrb. f. Kinderh., 1905, lxi, 687.

Observation 5.—F. D., now 8 months old; same child as in Observation 3.

A preliminary study of specimens of the rectal contents showed the presence of cocci, colon bacilli, *B. acidophilus*, *B. aerogenes capsulatus*, and a few gram-positive bacilli containing oval spores.

May 1, 1912. Food: fat, 2.6; sugar, 4.5; protein, 5.0. Within three days the formula was changed to fat, 2.6; sugar, 2.5; protein, 6, and the gram-stained slides prepared from the fecal material showed a very mixed picture. There were gram-positive cocci, very long gram-positive bacilli, some vacuolated gram-positive bacilli in parallel pairs or in small groups, large gram-positive bacilli containing spores, small ovals containing spores, gram-negative bacilli like the colon varieties, large gram-negative, granular bacilli, and some gram-negative bacilli containing spores. The amount of gas found in the fermentation tubes was very small, the milk tubes were coagulated but only very slightly peptonized. During the following week the picture remained the same, the bacteria cultivated from the feces including streptococci, staphylococci, *B. coli communis*, *B. bulgaricus*, and *B. mesentericus*. *B. bifidus* grew in the fermentation tubes. The only change observed during the following week was a decided increase in the amount of peptonization in the milk and gelatin cultures inoculated from the feces, and, in the smears, the number of spore-bearing bacilli increased comparatively, though all the other forms remained.

May 20. "Synthetic" food, fat, 2.06; sugar, 1.8; protein, 6. For two days there was practically no change distinguishable. At the end of that time, although the reaction of his rectal contents remained distinctly acid to litmus paper, the spore-bearing bacilli increased somewhat in numbers, *B. bulgaricus* had disappeared, the colon bacilli were less numerous, and bifidus forms were very few.

May 23. On the third day a rise in temperature occurred and the carbohydrate content of the food was increased to 5 per cent. the following morning, the protein remaining at 6 per cent. The spore-bearing gram-positive bacilli, isolated as *B. mesentericus*, still dominated the picture, bifidus forms also being present. As the temperature continued high, castor-oil was administered on May 25.

For a period of twenty days this child was fed on a mixture made with ripened milk, and *B. bulgaricus* was present in his rectal contents throughout that time. In one of the other studies (Observation 1) the period in which ripened milk was used in the food lasted twenty-three days, and in Observation 4 it lasted eighteen days. In neither of these cases, however, did the acid reaction of the rectal contents continue until the appearance of the fever, nor did *B. bulgaricus* appear in the feces throughout the entire period of feeding with ripened milk. This prolonged period of acidity did seem to delay the increase of proteolytic bacteria, though it did not entirely prevent their development. It would also seem that since all the clinical symptoms accompanying the end of this observation were as marked as they had been in the other four, the proteolytic bacteria were not the cause of those symptoms, but only the inevitable result of a comparatively high protein content in the food, and not, in themselves, harmful.

The slow increase of the proteolytes and the persistence of *B. bifidus* would seem to exemplify the statement of Tissier[11] that the rôle of *B. bifidus* is to keep the intestinal tube acid enough to arrest the development of many abnormal invaders, and to remove the proteoses necessary

11. Tissier, H.: Ann. de l'inst. Pasteur, 1905, xix, 119 and 272.

for the development of the latter. The presence of *B. bulgaricus* helped to increase the acidity, but even the combined acidity of the two was insufficient to prevent *B. mesentericus,* which attacks all proteins, from developing.

SUMMARY

To sum up the results of these five observations, we find that the varieties of bacteria identified as present in the rectal contents of the five children before and during the period of study included the following: *Albococcus, Micrococcus ovalis* or *Enterococcus,* a streptococcus proteolyzing milk, a streptococcus not proteolyzing milk, *B. coli communis; B. coli communior; B. lactis aerogenes; B. acidophilus; B. bifidus; B. bulgaricus; B. fluorescens,* liquefying gelatin. *B. dysenteriae* (Shiga) was found in one case.

During the periods of high carbohydrate in the food the cocci, colon bacilli, acidophilus and bifidus bacilli were most numerous; sometimes *B. aerogenes capsulatus* appeared.

During the periods of high protein content in the food, *B. mesentericus* gained the ascendancy, *B. aerogenes capsulatus* sometimes persisted, and the colon bacilli were increased in numbers. But the acidophilus and bifudus bacilli did not entirely disappear, probably because the change in the food was not complete nor prolonged enough.

Bacteria introduced with the food (*B. fluorescens, B. bulgaricus, B. subtilis, B. megatherium*) were found in the feces within a period varying from twenty-four to seventy-two hours.

The transition in the flora from one period to another was always gradual, never abrupt, recognizable changes requiring forty-eight to seventy-two hours to develop.

The return to the bacterial picture present at the beginning of the observation, which may be assumed to be the normal for that particular infant, was accomplished in from seven to ten days after the end of the study and subsequent catharsis.

As regards the children studied a second time, neither one gave any evidence of a more rapid reaction during the second observation than he had shown during the first.

PART IV.—OBSERVATIONS ON METABOLISM

ANGELIA M. COURTNEY
Fellow of the Rockefeller Institute
ASSISTED BY
JESSIE A. MOORE
NEW YORK

METHODS OF ANALYSIS

The methods used were mainly those described in preceding papers.[12] A few changes and additions are to be noted. In the determination of feces fat, a third portion of dried material was mixed with an excess of alcoholic solution of N/5

12. AM. JOUR. DIS. CHILD., 1911, i, 321-340; January, 1912, iii, 1-14.

sodic hydrate, thus binding the free fatty acids and leaving only neutral fat to be extracted. The values thus obtained for neutral fat are subtracted from those obtained from the simple extraction of the dried material, giving values for the free fatty acids present. Total ash was determined by heating in a platinum dish with small amounts of ammonium nitrate, cooling and weighing until weight is constant. For the determination of chlorid, the solid material was thoroughly mixed with dry sodium carbonate and charred, the alkali neutralized by nitric acid, the solution filtered off and titrated according to the Volhard method. Chlorids in the urine were also determined according to Volhard. The method for determining calcium has been described. Magnesium was determined in the filtrate remaining from the calcium determination by precipitating ammonium magnesium phosphate by addition of disodium phosphate, filtering through a Gooch crucible after an interval of several hours and heating the precipitate with a blast lamp until it is converted to magnesium pyrophosphate. Phosphates were determined in the urine by titration with uranium nitrate, potassium ferrocyanid being used as indicator.[13] The solid material, dried milk and feces, was ashed to whiteness in a platinum crucible with powdered magnesium oxid, the residue dissolved in 10 c.c. hot 5 per cent. hydrochloric acid, neutralized to phenolphthalein with 5 per cent. sodic hydrate and 0.5 to 1 c.c. excess added, again neutralized by 10 per cent. acetic acid containing 10 per cent. sodium acetate and 2 to 3 c.c. more acetate solution added.[13] The solution was then titrated with uranium nitrate as in case of urine.

PREPARATION OF FOOD MIXTURES

"Synthetic" Food Mixture.—A casein curd was obtained by allowing junket tablets to act on 4,000 c.c. of fat-free milk. The curd was drained through cheese cloth and washed four times with boiled water. A solution of the casein was effected in the following manner: The moist curd was ground in a mortar with successive small quantities of N/10 sodic hydrate and hot water until the mass resembled a thick boiled starch. (The alkali and water were sterilized by boiling.) A clear fluid solution of the casein was then effected by heating the paste for a few minutes in a double boiler. The solution of casein did not react alkaline, although it required 250 c.c. of sodic hydrate (1 gm. of the salt) to accomplish the solution. The final food mixture was made up by adding to the casein solution 200 c.c. of milk and the desired quantity of 32 per cent. cream. Boiled water was added to make up a volume of 1,500 c.c.; of these 1,260 c.c. were employed for feeding and the remaining 240 c.c. for analysis.

Other High Protein Food Mixtures.—The casein curd was prepared in the manner described in the preceding paragraph. The curd was then ground up and pressed through a fine sieve by the aid of 600 c.c. of ripened milk containing 2 per cent. fat. To this suspension boiled water, lactose, and 32 per cent. cream were added in desired proportion. The amount of fat-free milk employed for the curd, of lactose, and of cream varied for each feeding period in accordance with the desired formula; the quantity of ripened milk remained constant. The amount of protein in each mixture was calculated on the basis of average values obtained from the analysis of several samples of the curd obtained in the manner described in the preceding paragraph.

CASE 1.—Francis H. There were ten periods of observation beginning Sept. 14, 1911, and ending Jan. 1, 1912; each period represented a change in the food. During the first two he was on a normally-balanced diet the aim of which was to provide a standard for comparison with the other diets in which one of the constituents predominated, and the other two were given in a minimum quantity. The percentage composition of the food during the first period of nineteen days was 2.6 fat, 5.0 carbohydrate, and 2.4 protein; of the second standard period of twelve days, 2.6 fat, 3.0 carbohydrate, and 2.4 protein (*vide* Table 1). The daily calorific

13. Am. Vozárik, Ztschr. f. Phys. Chem., 1911-12, No. 76, v and vi, 426 and 433

intake of the food mixture of the first period contained 721 calories, and of the second period 690 calories. The general condition of the infant on this diet was fairly satisfactory. The average gain in weight was about 12 gm. per day in the first period, and about 5 gm. per day in the second period. The stools were very watery, contained some curds, were foamy, greenish and contained some mucus. The nitrogen balance was positive, reaching 1.2 gm. per day. The general composition of the urine indicated only a slight deviation from the normal in the first period, and scarcely any in the second period. The percentage of ammonia nitrogen in the urine was 8.5 of the total in the first period, indicating, perhaps, very slight acidosis. Creatin and creatinin output showed values differing little from those of the following periods. The ash retention in the first period was considerably higher than in the second, reaching the value of 2 gm. per day in the first, and 0.3 gm. in the second period. The stools presented a comparatively high total acidity, reaching in the first period the value of 903 and in the second period 779 per 100 gram of dried material.

In the third period lasting four days, and the fourth period lasting five days, the fat was removed from the food mixture in the third, and lowered to the proportion of 1.6 per cent. of the total food intake in the fourth period. The calorific intake was 567 calories in the third, and 649 calories in the fourth period. On this diet the appearance of the stools changed considerably. The color was copper-yellow, of watery appearance with considerable mucus, and with many hard curds. In the fourth period they gradually became granular, with many small fat curds, and the quantity of mucus then diminished. The general condition of the infant, as indicated by the body weight of the patient, was better in the third period than in the fourth, showing a gain of 25.7 gm. per day in the third, and a loss of 23.3 gm. per day in the fourth period. The nitrogen balance was positive in both periods, being 1 gm. per day in the third, and 0.7 gm. per day in the fourth. The composition of the urine in both periods indicates less acidosis than one noticed in the first two periods. Very striking were the fluctuations in creatin output; while the output of creatinin remained nearly constant.

This observation regarding creatin is rather in conflict with those made by Rose[14] in Professor Mendel's laboratory and by Folin.[15] It is not possible at the present moment to give an adequate explanation of the differences in the observations of Rose and of Folin on one hand and ours on the other. The considerable difference in the ages of the children may contain the reason for the discrepancy, or it may be occasioned by some accident of the observation.

The total mineral balance was less favorable during these two periods as compared with the first two. The chemical changes in the composition of the feces were not striking, the acid value per 100 grams being about the same as in the second period. As a significant distinction one may point out the proportion of soaps in the stools, which presented a much lower value than in the preceding periods.

To sum up, a food mixture composed of a high proportion of carbohydrate and low in fat resulted in a change in the general appearance of the stools, and in a fall of the mineral balance. There was noted also a marked change in the creatin output. The importance of the creatin values cannot be discussed at the present moment.

In the observations following the fourth period we aimed to change gradually the diet so as to raise principally the protein intake and to lower the fat and the carbohydrate. The highest protein intake was 6 per cent. of protein on the total volume of the food mixture.

During these periods the condition of the infant, as expressed by the daily gain in weight, was improved. The gain was 55 gm. per day the fifth, 64.8 gm. in the sixth, and 10.5 gm. per day in the seventh period.

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14. Mendel, L. B., and Rose, W. C.: Jour. Biol. Chem., 1911, x, 213, 265.
15. Folin, Otto, and Dennis, W.: Jour. Biol. Chem., 1912, xi, 3, 253.

There was little change in the composition of the urine (Table 2) which could be considered of significance; perhaps worthy of note is again the creatin output, which still remained high; in fact, it reached its highest value during the fifth period. During that period the total calorific intake was lower than that of any of the preceding periods. In the following period the calorific intake was raised to 900 from 500, and with this change there was noted a fall in the creatin and simultaneously a rise in the creatinin output. During the following period in which the protein intake was raised to a still higher level, and the carbohydrate intake slightly increased, there was noted a still greater fall in the creatin and a still higher rise in the creatinin output. Thus it seems that in this infant the creatin output diminished with the increase of the protein intake. The proportion of carbohydrate in the food apparently had less influence on the output of creatin and creatinin.

However, the high protein intake caused a very striking change in the character of the stools (Table 3). They became for the most part pasty, grayish-yellow, smooth; in other words, practically normal. The total acidity showed a marked fall from 900 in the first period to 148 in the seventh period. On the contrary, the proportion of soaps was greatly increased, and with it followed an increased mineral retention.

The nitrogen retention during these periods reached its highest values. It is worthy of note, that the very high retention did not last more than one or two days after the beginning of the very high protein intake, and reached its equilibrium generally on the third day.

The most significant is the eighth period of observation (November 16 to November 21). The food at that period was so changed as to contain the same or a slightly higher proportion of protein, as in the previous period, with a lower intake of carbohydrate and fat, so as to bring down the average daily calorific intake to 632 calories. On this diet the infant seemed to remain in a normal condition for three days. On the fourth day, he developed high temperature, and other symptoms which are described in the clinical part of this communication. From the standpoint of chemical metabolism, this period presented nothing significant that could distinguish it from the preceding period. Everything that was said about the peculiarities of the urine, stools, and general balance of the preceding period applies also to this period.

The lower average values for the balances of nitrogen and other constituents are principally due to the fact that the child refused food during the days of high fever.

The only very striking peculiarity of this period was the *retention of chlorids* beginning a few days immediately preceding the fever and continuing during the days following it.

In the following ninth period (December 12 to December 23) a change of the diet was again made in the way of diminishing the protein to a minimum and raising the carbohydrate to a maximum. During this period the condition of the child and the character of the stools and urine were practically the same as during the third period of observation, when the carbohydrate intake was at its maximum.

The food of this period differed from that of the preceding periods not only in the proportion of fat, protein, and carbohydrate, but also in containing for part of the time sodium phosphate, which was added to the daily food mixture. However, this was without any effect on the body temperature.

The tenth period (December 26 to January 1) was planned to be a repetition of the observations made in the eighth period, and the food was made up in exactly the same way. This food is referred to as the "synthetic" food. Under the influence of that food the child remained in perfectly normal condition for five days, and on the sixth day he again developed a marked rise in body temperature which lasted until the following day.

Again there was observed a retention of chlorids beginning a few days preceding the fever and lasting after the body temperature was restored to normal.

CASE 2.—The observations were made on Jacob S., aged 7½ months. The observations on this infant and also on Case 3 are divided into periods corresponding to food changes. These changes were planned to furnish definite evidence as to whether or not the "synthetic" food mixture was capable of disturbing the normal body temperature. With this in view the food intake was gradually modified so as to preserve approximately the same calorific intake by replacing the carbohydrate with protein until the maximum protein intake of 6 per cent. of the food mixture was reached.

The general changes in the composition of the urine and stools had the same character as in the periods of high protein intake of the first infant, namely, there was noted a gradual fall in the acidity of the stools and with it a rise in the proportion of soaps and general increase in the mineral balance. The nitrogen retention steadily increased until the maximum protein intake was reached. The child was gaining in weight continually, though slowly, and the total gain was about 350 gm.

When the highest protein intake of 6 per cent. per day was reached, the food was again changed to the one designated as "synthetic" mixture. On the fourth day of that régime the infant developed fever reaching 103.2 F. This fever continued for seven days until the food was changed. The general character of the stools, urine, and general metabolism presented nothing of significance that distinguished the period of "synthetic" diet from the immediately preceding period. Typical only was the retention of chlorids as noted in both observations on Case 1. The changes that are recorded in the last days of this period were not due to the character of the food, but to the administration of calomel and castor-oil, which caused free catharsis.

Two series of observations were made on Case 3, Francis D. The first one aimed simply to determine the capacity of the "synthetic" food mixture to cause a rise in body temperature (Table 5). There was no investigation made into the chemical metabolic changes. The results of this observation were in all respects confirmatory of the first three observations made on the other infants. Fever developed on the fourth day.

The second series of observations made on this infant was planned principally to ascertain whether the influence of the "synthetic" food mixture on the body temperature is a constant occurrence; during this period clinical observations were accompanied by a study of the chemical metabolism. Again on this occasion the changes of the diet aimed principally at raising the protein intake to a maximum of 6 per cent. of the milk formula. The food mixture contained 5 per cent. of protein when the infant was first placed in the metabolism bed. In the course of four days the maximum of 6 per cent. was reached, and this was continued for sixteen days. There was a constant gain in weight and a constant rise in the nitrogen retention. The general changes in the composition of the urine and feces were the same as in the other experiments. The most striking features were the fall in the total acidity of the feces, the rise in the proportion of soap, and the rise in the mineral balance.

After the child had been for sixteen days on the maximum protein intake, the diet was again changed to the "synthetic" food mixture. On the fourth day after this change there was again a marked rise of the body temperature which reached on the fifth day of the period 104 F. The addition of lactose, raising the carbohydrate to 5 per cent., had no effect on the temperature, though it was continued for two days. The condition of the infant, however, did not permit of prolonging the observation and on the seventh day of this period the "synthetic" food was discontinued. The general character of the urine and stools during this period did not present any striking differences from that of the previous ones, and those differences that did appear may be explained by looseness of the bowels produced by prolonged administration of milk of magnesia. There was again noted the usual retention of chlorids.

TABLE 2.—AVERAGE DAILY FOOD INTAKE

Case 1, Francis H.

Period	Dates	Composition of Food		Volume Intake c.c.	Fat, gm.	Carbohydrate, gm.	Protein, gm.	Nitrogen, gm.	Total Number Calories	Chlorids as NaCl, gm.	Phosphates as P_2O_5, gm.	Total Ash as Oxids, gm.	CaO, gm.
1	Sept. 14 to Oct. 3	Sixty-five per cent. milk, 5 per cent. lime water, barley water to volume, making fat 2.6 per cent., protein 2.4 per cent.; lactose added to make 5 per cent.		1,255	32.4	57.0	29.8	4.76	721	1.68	2.58	7.46	2.55
2	Oct. 4-14	Like that of Period 1, except that no lactose added, making carbohydrate 3 per cent.		1,260	33.6	48.5	27.4	4.54	690	1.68*	2.55	7.60	3.21
3	Oct. 16-19	Fat-free milk, cane-sugar added to make total carbohydrate 6 per cent.; protein 3.5 per cent.		1,260	0	75.5	41.3	6.61	567	1.57	2.77	9.86	3.65
4	Oct. 20-24	Mixture of fat-free and full milk, making 1.6 per cent. fat and 3.0 per cent. protein; cane-sugar to make 4.7 per cent. carbohydrate; 10 per cent. barley-water, 5 per cent. lime-water included.		1,260	20.0	59.6	34.8	5.57	649	1.88	2.40	8.88	3.01
5	Oct. 25-29	Three-fourths ordinary protein milk, ¼ barley-water, making fat 1.9 per cent., carbohydrate 2.3 per cent., protein 2.9 per cent.		1,230	23.0	28.0	35.7	5.71	504	1.26	2.21	7.71	2.80
6	Oct. 31 to Nov. 6	Protein milk made from casein of 2 liters full milk, 1 liter ripened fat-free milk and 120 c.c. water, making fat 3.6 per cent., carbohydrate 3.1 per cent., protein 5.6 per cent.		1,243	44.2	38.7	69.5	11.12	913	2.23	4.0	13.13	2.52
7	Nov. 14-16	Protein milk made from casein of 1 liter full milk, 1 liter ripened fat-free milk and 120 c.c. water, 4 drams maltose to day's food, making fat 3.5 per cent., carbohydrate 3.4 per cent., protein 3.9 per cent.		1,260	43.5	42.7	49.6	7.94	845	1.81	3.14*	10.28	2.72
8	Nov. 16-21	So-called synthetic food, fat 2.9 per cent., carbohydrate 1.5 per cent., protein 5.8 per cent. For description see text.	Daily Figures	1,260	31.8	18.5	71.6	11.46	705	.730†	3.60†	11.70	3.37†
				1,260	36.6	18.9	65.4	10.44	722	.....	....	10.58	....
				1,260	39.7	20.3	78.0	12.48	815	.....	....	11.62	....
				1,135	33.8	17.3	68.4	10.94	702	.....	....	9.85	....
				580	15.7	8.6	36.8	5.9	355	.....	....	5.47	....
9	Dec 12-16 16-20 20-23	Mixture fat-free and full milk, making fat 2 per cent., protein 2.5 per cent.; dextrimaltose added to make carbohydrate 6.4 per cent.; 20 per cent. barley-water and 5 per cent. lime-water included. In part of period (Dec. 16-20) 8,3 gm. mono- and disodium phosphate added to day's food.		1,260	26.2	72.4	31.0	4.96	732	1.59†	2.47†	6.99	1.56†
				1,260	20.6	85.0	31.3	5.0	728	.....	....	14.94	....
				1,260	29.9	85.9	31.0	4.96	818	.....	....	8.91	....
10	Dec. 26 to Jan. 1	So-called synthetic food, fat 2.1 per cent., carbohydrate 1.7 per cent., protein 6.3 per cent.	Daily Figures	515	10.6	8.6	31.2	4.99	480†	.587†	2.90†	4.78	3.18†
				1,045	27.9	18.7	63.7	10.19	...	.....	.....	7.45	....
				1,135	26.1	19.6	72.7	11.63	...	.....	.....	10.49	....
				1,184	23.8	19.6	82.5	13.20	...	.....	.....	9.94	....
				1,230	23.5	20.4	78.2	12.50	...	.....	.....	11.78	....
				180	....	....	12.1	1.94	...	.....	.....	1.01	....

Case 2, Jacob S.

Daily	1,184	23.8	19.6	82.5	13.20	...	.....	.....	10.49	....
	1,230	23.5	20.4	78.2	12.50	...	.....	.....	9.94	....
	180	....	....	12.1	1.94	...	.....	.....	11.78	....
									1.01	....

CASE 2, JACOB S.

1	Feb. 27-29	Mixture fat-free and full milk to make fat 1.45 per cent., protein 3.5 per cent., lactose added to make 5 per cent.; 2 dr. neutral maltose and 3½ dr. olive oil added to day's food.....		1,050	26.6	52.2	33.7	5.39	676	1.13	2.25	5.41	1.98
2	Feb. 29 to March 4	Fat 1.45 per cent., carbohydrate 4.5 per cent., protein 4 per cent., 3½ dr. olive oil added to day's food. For method of making up this formula and the four following see text.....		998	27.1	45.6	40.7	6.50	637	1.01	2.53	5.26	2.12
3	March 4-7	Fat 1.45 per cent., carbohydrate 4.0 per cent., protein 4.5 per cent., 3½ dr. olive oil added to day's food		1,007	29.1	40.5	42.6	6.82	647	1.19	2.48	5.47	2.28
4	March 7-10	Fat 1.45 per cent., carbohydrate 3.5 per cent., protein 5.0 per cent., 3½ dr. olive oil added to day's food		1,015	24.9	37.8	51.9	8.31	636	1.40	2.99	6.45	2.37
5	March 10-13	Fat 1.45 per cent., carbohydrate 3.0 per cent., protein 5.5 per cent., lime-water 5 per cent., 3½ dr. olive oil in day's food.....		1,025	24.3	32.8	57.0	9.12	628	1.23	3.22	6.66	2.74
6	March 13-18	Fat 1.45 per cent., carbohydrate 2.1 per cent., protein 6.0 per cent., lime-water 5 per cent., 1½ dr. olive oil in day's food.....		1,050	16.7	28.6	61.6	9.85	563	1.19	3.64	7.97	3.35
7	March 18-27	So-called synthetic food, fat 1.45 per cent., carbohydrate 1.8 per cent., protein 6.0 per cent., 1½ dr. olive oil added to day's food; 120 c.c. breast milk March 25 and 210 c.c. March 26.	Daily Figures	900	14.7	13.8	47.9	7.67	397	.327	2.49	6.13	2.77
				1,050	15.2	19.8	66.0	10.56	502	.574	3.44	7.66	2.77
				975	17.1	19.0	59.9	9.60	491	.515	2.98	7.54	3.44
				630	14.2	11.8	35.8	5.74	333	.242	1.98	4.34	2.08
				900	16.2	19.2	60.4	9.68	486	.463	3.22	6.66	2.93
				780	14.3	15.3	53.2	8.51	421	.434	2.82	6.27	2.66
				1,050	14.1	19.8	65.6	10.50	490	.642	3.49	7.75	3.76
				930	14.9	23.9	50.4	8.07	448	.400	2.74	6.29	2.62
				725	14.8	24.9	35.2	5.64	386	.300	1.90	4.08	1.69

CASE 3, FRANCIS D.

1	May 1	Fat 2.6 per cent., carbohydrate 4.5 per cent., protein 5.0 per cent., 2 dr. olive oil added to day's food		1,260	38.2	65.8	63.4	10.13	917	1.44	3.84	7.65	3.24
2	May 2-4	Fat 2.6 per cent., carbohydrate 3,5 per cent., protein 5.5 per cent., 2 dr. olive oil in day's food		1,260	38.0	46.0	71.4	11.42	877	1.49	4.12	9.34	3.71
3	May 4-19	Fat 2.6 per cent., carbohydrate 2.5 per cent., protein 6.0 per cent., 2 dr. olive oil in day's food. For method of making up this and two preceding formulæ see text		1,253	38.6	33.8	74.9	11.98	846	1.47	4.23	10.50	4.12
4	May 20-24	So-called synthetic food, fat 2.6 per cent., carbohydrate 1.8 per cent., protein 6.0 per cent. 2 dr. olive oil in day's food; 36 gm. lactose added to day's food May 23-24.	Daily Figures	1,260	36.2	22.0	73.4	11.75	739	.253	3.75	8.65	3.36
				1,260	41.4	22.0	74.8	11.95	794	.360	3.95	9.95	4.17
				1,260	40.2	21.9	71.2	11.40	767	.256	3.62	9.11	3.69
				1,260	37.5	21.8	76.5	12.24	764	.359	1.13	9.60	3.85
				1,260	36.4	58.2	69.0	11.06	863	.167	3.61	7.99	3.39

*Estimated. †Average.

TABLE 3.—URINE CONSTITUENTS. AVERAGE DAILY VALUES

CASE 1, FRANCIS H.

Period	Dates	Volume, c.c.	Specific Gravity	Indican	Total Nitrogen, gm.	Ammonia Nitrogen, gm.	Ammonia Nit. Per cent. Total N.	Kreatinin Nitrogen, gm.	Kreatin Nitrogen, gm.	Inorg. Sulphates as H_2SO_4, gm.	Ethereal Sulphates as H_2SO_4, gm.	Total Sulphates as H_2SO_4, gm.	Chlorids as NaCl, gm.	Phosphates as P_2O_5, gm.	Total Ash as Oxids, gm.	CaO, gm.
1	Sept. 14 to Oct. 3	426	1.010½	Gen. Negative	2.81	.240	8.5	.063	.023	.362	.123	.485	.817	.587	1.44	.079
2	Oct. 4-14	541	1.011	Neg. to High 10+	3.18	.118	3.7	.055	.011	.472	.131	.603	1.179	.635	2.72	....
3	Oct. 16-19	547	1.013	Negative	4.66	.152	3.2	.043	.047	.722	.122	.844	1.549	.731	3.39	....
4	Oct. 20-24	663	1.011	Negative	4.29	.073	1.7	.050	.078	.772	.080	.852	1.894	.729	4.45	.673
5	Oct. 25-29	703	1.011	Faint trace or neg.	4.78	.132	2.8	.042	.108	.695	.139	.834	1.791	.577	2.48	....
6	Oct 31 to Nov. 6	488	1.018	Neg. or small trace	7.45	.342	4.6	.064	.055	1.078	.133	1.211	1.392	.832	3.21	.124
7	Nov. 14-16	475	1.016	Nearly negative	5.36	.158	3.0	.075	.008	.747	.188	.935	.806	.612	2.84	....
8	Nov. 16-21	550	1.012	Faint trace	5.30	.137	2.6	.071	.025	.671	.219	.890	.323	.636	1.69	....
	Daily Figures	490	1.016	Faint trace	7.52	.178	2.4	.070	.059	1.129	.040	1.169	0	.639	1.65	....
		530	1.016	Trace	8.76	.279	3.2	.074	.008	1.122	.172	1.294	0	.780	1.59	....
		475	1.018	8-10	9.34	.326	3.4	.070	.025	.798	.558	1.356	0	.722	1.33	....
		350	1.019	16-20	7.36	.340	4.6	.081	.004	1.22	.165	1.385	0	.717	1.44	....
9	Dec. 12-16	514*	1.013*	Negative	3.35	.189	5.7	.043	.029	.523	.087	.610	1.53	.516	3.45	2.30*
	16-20	...	.....	.....	3.08	.187	5.7	.041	.008	.492	.055	.547	1.55	.757	4.31	....
	20-23	...	.....	.....	3.30	.158	4.8	.041	.042	.538	.080	.618	1.98	.566	4.07	....
10	Dec. 26 to Jan. 1	255	1.021*	Negative	3.70	.110	3.0	.044	.010	.632	.045	.677	.513	.582	2.61	.028*
	Daily Figures	330	.....	Large trace	6.65	.337	5.1	.055	.023	.904	.062	.966	.292	.747	1.77	....
		430	.....	Trace	7.98	.344	4.3	.043	.020	.982	.019	1.001	.066	.525	1.52	....
		410	.....	Faint trace	9.10	.327	3.6	.044	. 0	1.185	.017	1.202	0	.665	1.31	....
		390	.....	8-10	8.80	.405	4.6	.054	.027	1.124	.011	1.135	0	.642	1.72	....
		355	.....	Trace	7.10	†	...	.047	....	1.185	.094	1.279	0	.686	1.77	....

CASE 2, JACOB S.

1	Feb. 27-29		493	1.013½	Small trace to neg.	2.83	.070	2.5	.041	.038	.456	.051	.507	.870	.578	3.24	.018
2	Feb. 29 to March 4		460	1.013	Neg. very high or faint trace	4.38	.146	3.3	.044	.018	.602	.085	.687	.907	.570	1.97	.042
3	March 4-7		410	1.014	Neg. to faint trace	4.80	.166	3.5	.043	.019	.741	.044	.785	.997	.558	1.61	.025
4	March 7-10		418	1.016½	Neg. or small trace	5.86	.326	5.6	.038	.025	.889	.055	.944	.843	.670	2.03	.018
5	March 10-13		458	1.019	Gen. consid. 5-20	6.44	.198	3.1	.034	.027	.969	.069	1.038	1.053	.704	1.63	.030
6	March 13-18		473	1.018	Trace to high 10-15	7.66	.305	4.0	.029	.046	1.157	.079	1.236	1.116	.752	2.06	.049
7	March 18-27	Daily Figures	435	1.014½	Consid. 5	6.00	.226	3.8	.038	.033	.834	.106	.940	.721	.597	1.60	....
			445	1.018	Consid. 5	6.32	.133	2.1	....	....	.923	.114	1.037	.297	.651	....	....
			490	1.019	High 20-30	7.83	.187	2.4	.043	.031	1.063	.068	1.131	.348	.756	1.65	....
			390	1.018½	Consid. 5	6.42	.206	3.2	.046	.032	.952	.091	1.043	.462	.611	1.26	....
			230	1.023	Consid. 5	5.24	.187	3.6	.048	.042	.768	.021	.789	.191	.650	1.02	....
			270	1.022½	Small trace	6.25	.215	3.4	.055	.045	.907	.038	.945	.080	.622	1.05	.024
			370	1.015	Faint trace	5.17	.151	2.9	.051	.027	.752	.037	.789	.077	.416	.908	....
			345	1.016½	Faint trace	5.69	.182	3.2	.048	.026	.819	.095	.914	.092	.438	.973	....
			250	1.019	Negative	4.85	.186	3.8	.045	.034	.664	.049	.713	0	.547	.593	....

CASE 3, FRANCIS D.

1	May 1		440	1.017	Negative	6.38	.287	4.5	.035	.037	.965	.050	1.014	.573	1.433	2.53	.101
2	May 2-4		395	1.021	Negative	7.54	.381	5.1	.034	.036	1.151	.059	1.209	.888	1.53	2.84	.102
3	May 4-19		388	1.022	Mostly neg. or faint trace	7.87	.359	4.6	.031	.032	1.177	.055	1.232	.774	1.32	2.53	.111
4	May 20-24	DailyFigures	340	1.023	5	7.65	.285	3.7	.039	.030	1.11	.060	1.170	.179	1.13	2.16	....
			260	1.022½	Faint trace	4.79	.123	2.6	.027	.028	.712	.043	7.55	.015	.753	1.46	.018
			395	1.018½	Considerable trace	7.53	.236	3.1	.032	.017	1.105	.067	1.172	0	1.12	2.01	....
			470	1.018	Faint trace	8.46	.263	3.1	.033	.017	1.270	.055	1.325	0	1.36	2.51	....
			380	1.021	Considerable trace	7.37	.268	3.6	.043	.004	1.114	.109	1.223	0	1.99	2.13	....

*Average. †Alkaline.

Indican.—The figures in this column indicate color percentages; undiluted Fehling's solution being taken as 100.

It will be noted that in Case 1 during the first observation, there was no excess of indican until the fourth day of the "synthetic" food; in the second period of observation there was no excess until the fifth day of the same food.

In Case 2 the indican was variable before the "synthetic" period, sometimes being quite high. The highest point was reached on the third day of "synthetic" food while marked constipation was present.

In Case 3 it was never in excessive amount during the long period antecedent to "synthetic" food, but it was high during that period. In the second period of observation only traces of indican were present at any time.

Sugar.—Tests for sugar were made only occasionally, as when the specific gravity was high or the sugar intake considerably increased. In no case was sugar found in the urine.

Albumin.—Daily examinations were made in all cases. In Cases 1 and 2 it was invariably absent. In Case 3 a considerable trace was noted but once, in the fifth day of the "synthetic" food.

TABLE 4.—COMPOSITION OF FECES. AVERAGE DAILY VALUES

Case 1, Francis H.

Period	Dates	Dried Weight, gm.	Dried Weight, per cent. of Moist.	Water in Feces, c.c.	Total Nitrogen, gm.	Total Nitrogen, % Dried Weight.	Chlorid as NaCl, gm.	Phosphates as P_2O_5, gm.	Total Ash as Oxids, gm.	Total Ash % of Dried Weight	CaO, gm.	Total Fat, gm.	Total Fat, per cent. Dried Weight	Neutral Fat, gm.	Neutral Fat per cent. Total Fat	Free Fatty Acids, gm.	Fatty Acids per cent. Total Fat	Soap Fat, gm.	Soap Fat, per cent. Total Fat	Total Acidity for 24 Hours c.c. N/10 NaOH	Total Acidity per 100 gm. Dried Wt.	Volatile Acids, 24 Hours, c.c. N/10 NaOH	Volatile Acids per 100 gm. Dried Wt.
1	Sept. 14 to Oct. 3	19.9	7.8	251	.782	4.0	.60	.92	3.98	20.0	1.28	6.96	34.7	4.72	66.2	1.18	16.8	1.06	17.0	181.6	903	118.6	639
2	Oct. 4-14	15.4	8.0	191	.707	4.6	.49	.80	4.56	29.6	1.34	4.61	29.5	2.94	63.6	.80	16.1	.87	20.3	119.9	779	137.3	907
3	Oct. 16-19	16.8	8.4	195	.922	5.5	.19	1.53	5.93	35.4	2.33	.43	3.9	.43	100.	.....	....	.....	....	133.3	799	110.0	658
4	Oct. 20-24	12.4	8.9	128	.587	4.7	.23	1.08	4.07	32.8	1.44	1.77	14.2	1.30	72.0	.25	16.2	.22	11.8	93.1	752	112.8	872
5	Oct. 25-29	7.7	16.2	40	.340	4.4	.05	0	2.87	37.0	1.27	1.23	15.6	.60	50.7	.12	7.9	.51	41.4	13.3	169	68.9	902
6	Oct 31 to Nov. 6	16.6	16.5	88	.663	4.0	.09	1.89	6.06	36.4	2.73	3.75	22.8	1.08	29.6	.14	4.3	2.53	66.1	25.6	148	128.0	757
7	Nov. 14-16	13.5	18.0	73	.594	4.4	.02	1.47	4.90	36.2	1.96	2.15	17.3	.65	27.6	.13	6.7	1.37	65.7	40.3	148	125.5	927
8	Nov. 16-21	15.0	13.7	95	.547	3.6	.17	1.87*	6.05	40.3	2.62*	2.72	18.1	1.38	50.8	.03	.2	1.31	48.1	52.6	351	122.0	812
	Daily Figures	11.7	21.0	44	.336	2.9	.02	....	4.66	39.8	...	4.53	38.6	.88	19.4	.15	3.1	3.50	77.5	76.3	65	93.5	797
		15.4	24.4	48	.443	2.9	.02	....	5.05	32.8	...	6.82	44.2	1.81	26.5	.63	9.3	4.38	64.2	19.0	123	148.5	964
		9.6	32.7	20	.296	3.1	0	....	3.18	33.2	...	4.16	43.4	.87	20.9	.40	9.7	2.89	69.4	8.9	93	53.9	562
		35.6	22.9	120	.856	2.4	0	....	10.85	30.6	...	19.20	54.0	6.16	32.0	.96	5.0	12.08	63.0	78.0	219	240.8	628
9	Dec. 12-16	12.9	11.7	99	.609	4.7	.11*	1.34*	3.49	26.9	1.91*	2.29	17.8	1.60	70.2	.35	15.4	.34	14.4	71.8	551	130.9	1,012
	16-20	12.5	8.2	142	.511	4 1	...	....	4.58	36.5	...	2.06	16.4	1.55	73.5	.48	24.9	.03	1.6	84.2	666	114.6	931
	20-23	11.8	11.1	96	.502	4.3	...	....	3.62	30.9	...	2.15	18.1	1.05	49.0	.43	18.4	.66	32.6	59.4	505	117.4	1,015
10	Dec. 26 to Jan. 1	3.1	14.6	18	.207	6.8	.08*	1.88*	.80	26.3	3.55*	.88	29.0	.42	48.0	.22	24.8	.24	27.2	6.7	218	106.2	3,490
	Daily Figures	16.5	20.8	63	.807	4.9	...	....	5.38	32.7	...	2.75	16.7	1.20	43.7	.26	9.6	1.29	46.7	23.1	140	137.8	838
		20.0	15.3	111	.960	4.8	...	....	7.07	35.4	...	3.46	17.3	2.46	71.1	0	0	1.00	28.9	21.2	106	188.0	943
		12.0	15.4	66	.616	5.1	...	....	3.68	30.8	...	2.22	18.6	.90	40.3	0	0	1.32	53.7	32.5	272	118.0	988
		25.5	18.1	116	1.188	4.7	...	....	8.83	34.6	...	5.72	22.4	2.52	44.2	.59	10.3	2.61	45.5	61.1	239	183.0	718
		22.9	20.3	90	.897	3.9	...	....	5.72	25.0	...	8.02	35.0	5.99	74.9	2.03	25.1	0	0	100.8	440	166.5	728

*Average.

Case 2, Jacob S.

1	Feb. 27-29	11.6	15.9	62	.672	5.8	.04	1.25	3.35	28.9	1.58	1.53	13.1	.70	45.4	.58	37.8	.26	16.8	51.4	442	99.0	853
2	Feb. 29 to March 4	8.7	21.2	32	.506	5.8	.02	1.13	2.54	29.4	1.42	1.45	16.7	.73	50.3	.02	1.4	.70	48.3	22.0	254	92.6	1,068
3	March 4-7	15.4	14.8	89	.855	5.6	.06	1.66	4.12	26.8	2.22	3.56	23.2	1.79	50.2	.97	27.1	.81	22.7	77.4	504	135.6	883
4	March 7-10	10.8	15.5	59	.685	6.4	.12	1.55	3.22	29.8	1.75	.74	6.8	.45	60.8	0	0	.29	39.2	33.1	307	109.0	1,011
5	March 10-13	9.8	26.9	27	.546	5.6	.05	1.61	3.41	34.7	1.82	.73	7.4	.30	41.1	.07	9.6	.36	49.3	3.4	35	93.3	951
6	March 13-18	11.5	31.4	25	.576	5.0	.04	1.81	4.18	36.4	2.52	1.28	11.1	.42	32.8	0	0	.86	67.2	—3.6	—31	112.2	975
7	March 18-27	9.2	29.1	23	.450	4.9	.03	1.58	3.67	39.7	1.98	.83	9.0	.14	16.7	0	0	.69	83.3	—5.5	—60	73.9	801
	Daily Figures	5.2	33.8	10	.264	5.0	.01	.62	2.12	40.5	1.15	5	2.9	.12	75.9	0	0	.04	24.1	—4.8	—91	119.0	2,275
		8.6	32.4	18	.430	5.0	.03	1.46	3.55	41.3	1.88	1...3	13.5	.27	23.0	.06	5.2	.83	71.8	0	0	104.0	1,213
		46.7	21.6	170	2.519	5.4	.17	4.66	11.25	24.1	6.22	10.84	23.2	7.66	70.7	.14	1.3	3.04	28.0	168.3	360	336.0	719
		28.1	16.9	138	2.454	8.7	.17	1.92	3.86	13.7	2.06	5.04	17.9	4.98	98.9	.06	1.1	0	0	183.6	652	154.0	548
		26.8	13.9	166	2.411	9.0	.25	2.00	4.55	17.0	2.60	5.16	19.3	4.76	92.2	0	0	.40	7.8	245.0	916	177.2	662
		21.4	13.5	137	1.675	7.8	.27	1.62	3.56	16.7	1.90	3.33	15.6	3.05	91.7	.28	8.3	0	0	120.0	562	168.8	790
		29.4	13.3	192	2.233	7.6	.51	2.10	4.89	16.6	2.32	5.97	20.3	5.41	90.6	0	0	.56	9.4	184.5	627	154.4	524
		20.5	13.6	130	1.683	8.2	.38	1.26	3.00	14.6	1.35	3.37	16.4	2.20	65.3	1.09	32.6	.08	2.4	113.8	555	103.5	504

Daily Figures	21.4	13.5	137	1.675	7.8	.27	1.62	3.56	16.7	1.90	3.33	15.6	3.05	91.7	.28	8.3	0	0	120.0	562	168.8	790
	29.4	13.3	192	2.233	7.6	.51	2.10	4.89	16.6	2.32	5.97	20.3	5.41	90.6	0	0	.56	9.4	184.5	627	154.4	524
	20.5	13.6	130	1.683	8.2	.38	1.26	3.00	14.6	1.35	3.37	16.4	2.20	65.3	1.09	32.6	.08	2.4	113.8	555	103.5	504

CASE 3, FRANCIS D.

1	May 1		20.2	18.4	90	.785	3.9	.10	.88	3.54	17.5	2.34	9.53	47.1	1.46	15.2	.44	4.7	7.63	80.1	40.5	200	162.4	803
2	May 2-4		15.4	17.5	72	.559	3.7	.10	.85	3.34	21.6	1.87	6.[illegible]	40.9	1.54	24.4	.05	.7	4.72	74.9	26.6	173	203.0	1,318
3	May 4-19		17.8	13.5	114	.694	3.9	.20	1.49	4.87	27.3	2.73	5.2[illegible]	29.6	1.01	19.2	.07	1.3	4.19	79.5	29.6	166	131.8	740
4	May 20-24		13.8	12.3	98	.626	4.6	.27	1 30	3.81	27.7	2.18	4.47	32.5	1.22	27.4	0	0	3.25	72.6	23.8	173	124.5	907
		Daily Figures	12.1	13.2	79	.605	5.0	.18																
			27.3	11.0	220	1.470	5.4	.62	.86	2.42	20.1	1.26	4.20	34.8	1.79	42.6	.59	14.1	1.82	43.3	50.3	417	125.0	1,038
			17.9	9.3	174	1.013	5.7	.75	1.98	6.06	22.2	3.25	9.30	33.6	4.34	46.7	3.99	42.9	.97	10.4	139.0	509	320.0	1,173
			25.9	11.4	201	1.422	5.5	.46	1.11	3.57	20.0	1.78	5.42	30.3	2.70	49.8	.99	18.2	1.73	32.0	111.1	623	182.8	1,023
									1.54	4.48	17.3	2.14	6.91	26.7	4.50	65.2	0	0	2.41	34.8	163.0	631	204.0	789

DESCRIPTION OF FECES

CASE 1, FRANCIS H.

1. Sept. 14-Oct. 3.—Thin, generally very watery, containing fat curds and few small hard curds, greenish-yellow, sometimes foamy; 8-12 stools daily.
2. Oct. 4-14.—Becoming more solid than in Period 1, more finely granular, 7-9 stools daily.
3. Oct. 16-19.—Orange-yellow, pasty or watery, containing hard curds and considerable mucus; 11-13 stools daily.
4. Oct. 20-24.—Watery or pasty, smooth and finely granular, containing small fat and protein curds, less mucus than in Period 3; 8-10 stools daily.
5. Oct. 25-29.—Mostly formed but soft, yellow-gray, smooth; 3-4 stools daily.
6. Oct. 31-Nov. 6.—Mostly formed, smooth, harder than in Period 5, portions watery or pasty, granular; 4-6 stools daily.
7. Nov. 14-16.—About as in Period 6; 4-5 stools daily.
8. Nov. 16-21.—After first day formed, hard and dry, containing fragments of hard curds; 3-6 stools daily.
9. Dec. 12-23.—Pasty or watery, containing fat curds, hard curds, and mucus, acid and rancid; 4-10 stools daily; more solid during last three days with less mucus.
10. Dec. 26-Jan. 1.—At first formed and semi-formed, rather soft and mealy, becoming hard and dry. After castor-oil was given largely watery and pasty, with small hard curds; 4-7 stools daily.

CASE 2, JACOB S.

1. Feb. 27-29.—Pasty, slightly formed, partly fluid, granular with fat curds, partly greenish; 4 stools daily.
2. Feb. 29-March 4.—Mostly formed, yellow-gray, smooth; 1-5 stools daily.
3. March 4-7.—More watery than in Period 2, foul, partly greenish, small part formed, 2-5 stools daily.
4. March 7-10.—As in preceding period, but generally more formed; 2-3 stools daily.
5. March 10-13.—Formed and hard; foul; 3-6 stools daily.
6. March 13-18.—As in preceding period, often with traces of blood; 3-7 stools daily.
7. March 18-27.—As in preceding period; 2-4 stools daily, until after castor-oil was given, then thin, pasty and watery, containing fragments of hard curds and mucus, generally greenish; 7-8 stools daily.

CASE 3, FRANCIS D.

1. May 1.—Formed, smooth, portion dry and hard, larger part soft, yellow-gray, 4 stools.
2. May 2-4.—As in Period 1; 1-4 stools daily.
3. May 4-19.—For first six days as in Periods 1 and 2, after that larger part thinner and less formed, 1-4 stools daily.
4. May 20-24.—Mostly watery and pasty, containing hard curds and often mucus, in increasing amount, partly greenish; about 3 stools daily.

TABLE 5.—BALANCES. AVERAGE DAILY VALUES

Case 1, Francis H.

Period	Dates	Total Nitrogen Retained, gm.	Nitrogen Retained, per cent. Intake	Nitrogen Retained, per cent. Absorbed	Nitrogen Absorbed, per cent. Intake	Total Fat Absorbed, gm.	Fat Absorbed, per cent. of Intake	Chlorid as NaCl Retained, gm.	Phosphates as P_2O_5 Retained, gm.	Total Ash as Oxids Retained, gm.	CaO Retained, gm.	Gain or Loss in Body Weight, gm.	Weight Beg. and End of Period, gm.
1	Sept. 14 to Oct. 3	+1.17	24.5	29.4	83.5	+25.5	78.6	+.258	+1.07	+2.04	+1.19	+ 11.7	4,330 4,553
2	Oct. 4-14	+ .65	14.4	17.1	84.7	+29.0	86.5	+.014	+1.12	+ .32	+1.87	+ 4.6	4,637 4,683
3	Oct. 16-19	+1.03	15.6	18.1	86.2	0	....	—.17	+ .51	+ .54	+1.32	+ 25.7	4.781 4,858
4	Oct. 20-24	+ .69	12.4	13.9	89.6	+18.2	91.0	—.25	+ .59	+ .36	+ .90	— 23.3	4,884 4,791
5	Oct. 25-29	+ .60	10.4	11.1	94.1	+21.8	94.8	—.58	+1.63	+2.36	+1.53	+ 55.3	4,372 4,593
6	Oct 31 to Nov. 6	+3.01	27.0	28.7	94.2	+40.5	91.6	+.75	+1.28	+3.86	— .33	+ 64.8	4,605 4,994
7	Nov. 14-16	+1.99	25.1	27.1	92.7	+41.3	95.0	+.98	+1.06	+2.54	+ .76	+ 10.5	4,995 5,016
8	Nov. 16-21	+5.62	49.1	51.4	95.3	+29.1	91.5	+.588*	+1.027*	+3.97	+ .75*	+ 47.0	5,016
	Daily Figures	+2.58	24.7	25.5	96.7	+32.1	87.9	.....	.....	+4.27	.....	+ 1.0	5,063
		+3.28	26.3	27.3	96.5	+32.9	82.8	.....	.....	+4.98	.....	+ 72.0	5,064
		+1.30	11.9	12.3	97.3	+29.6	87.7	.....	.....	+5.35	.....	— 70.0	5,136
		—2.32	....	....	84.9	— 3.5	....	.....	.....	—6.82	.....	—497.0	5,066 4,569
9	Dec. 12-16	+1.00	20.2	23.1	87.9	+23.9	91.4	—.05	+ .61	+ .05	— .35*	— 30.3	5,206 5,085
	16-20	+1.41	28.2	31.4	89.9	+18.6	90.4	—.07	+ .37	+6.05	.....	+ 50.3	5,085 5,286
	20-23	+1.16	23.3	26.0	90.1	+27.8	93.1	—.50	+ .56	+1.22	.....	+ 9.0	5,286 5,313
10	Dec. 26 to Jan. 1	+1.08	21.8	22.7	96.1	+ 9.72	91.6	+.358*	+ .384*	+1.37	— .40*	—276.0	5,265
	Daily Figures	+2.73	26.8	29.2	92.1	+25.2	90.2	.....	.....	+ .30	.....	+226.0	4,989
		+2.69	23.1	25.2	91.8	+22.6	90.3	.....	.....	+1.90	.....	+ 27.0	5,215
		+3.48	26.4	27.7	95.3	+21.6	90.6	.....	.....	+4.95	.....	— 33.0	5,242
		+2.51	20.1	22.2	90.6	+17.8	75.7	.....	.....	+1.23	.....	+109.0	5,209
		—6.06	....	....	53.8	— 4.3	....	.....	.....	—5.88	.....	—697.0	5,318 4,621

*Average.

*Average.

CASE 2, JACOB S.

1	Feb. 27-29		+1.89	35.1	40.0	87.7	+25.1	94.2	+.22	+ .42	—1.18	+ .38	+ 92.0	3,968 4,151
2	Feb. 29 to March 4		+1.62	25.0	27.0	92.4	+25.6	94.8	+.08	+ .83	+ .75	+ .66	+ 14.0	4,151 4,208
3	March 4-7		+1.17	17.1	19.5	87.6	+25.5	87.9	+.131	+ .268	— .26	+ .04	— 6.0	4,208 4,191
4	March 7-10		+1.77	21.3	23.2	91.8	+24.2	97.2	+.437	+ .78	+1.20	+ .61	+ 29.0	4,191 4,278
5	March 10-13		+2.13	23.6	25.1	94.0	+23.6	97.1	+.128	+1.01	+1.63	+ .89	+ 16.0	4,278 4,326
6	March 13-18		+1.62	16.4	17.4	94.2	+15.4	92.3	+.029	+1.08	+1.74	+ .78	+ 19.0	4,326 4,423
7	March 18-27		+1.22	15.9	16.9	94.2	+13.8	94.5	—.42	+ .31	+ .86	+ .80	— 75.0	4,423
		Daily Figures	+3.98	37.7	38.7	97.8	+15.1	99.0	+.28	+2.17	....	....	+ 60.0	4,348
			+1.34	14.0	14.6	95.6	+15.9	93.4	+.14	+ .77	+2.34	+1.56	— 19.0	4,408
			—3.20	....	....	56.1	+ 3.4	23.6	—.39	—3.29	—8.17	—4.14	—313.0	4,389
			+1.98	20.5	27.4	74.9	+11.1	68.6	+.11	+ .65	+1.78	+ .88	— 21.0	4,076
			—. 15	....	....	71.7	+ 9.11	63.8	+.10	+ .20	+ .67	+ .04	— 35.0	4,055
			+3.66	34.8	41.4	84.0	+10.8	76.4	+.29	+1.46	+3.28	+1.86	+ 21.0	4,020
			+ .15	1.9	2.6	72.4	+ 8.9	60.0	—.20	+ .20	+ .43	+ .30	— 46.0	4,041
			— .90	....	....	70.2	+11.4	77.4	—.08	+ .09	+ .49	+ .34	—127.0	3,995 3,868

CASE 3, FRANCIS D.

1	May 1		+2.96	29.2	31.7	92.2	+28.6	75.2	+.768	+1.53	+1.58	+ .80	+147.0	4,725 4,872
2	May 2-4		+3.32	29.0	30.5	95.2	+31.7	83.5	+.505	+1.74	+3.16	+1.74	— 41.0	4,872 4,790
3	May 4-19		+3.42	28.5	30.3	94.3	+33.3	86.4	+.502	+1.42	+3.10	+1.29	+ 18.0	4,790 5,077
4	May 20-24		+3.47	29.5	31.2	94.7	+31.7	87.7	—.192	+1.32	+2.68	+1.18	+ 71.0	5,077
		Daily Figures	+6.56	54.9	57.8	94.9	+37.2	89.8	+.161	+2.34	+6.07	+2.90	— 61.0	5,148
			+2.40	21.1	24.2	87.1	+30.9	76.9	—.360	+ .52	+1.04	+ .44	— 83.0	5,087
			+2.77	22.6	24.6	91.8	+32.1	85.7	—.390	+1.66	+3.51	+2.07	— 8.0	5,004
			+2.27	20.5	23.6	87.1	+29.5	81.1	—.295	+ .98	+1.38	+1.25	—203.0	4,996 4,793

TABLE 6.—PRELIMINARY OBSERVATIONS ON CASE 3

Period	Dates	Composition of Food	Body Weight, gm.	Volume Urine, c.c.	Specific Gravity of Urine	Indican in Urine	Intake Chlorids as NaCl, gm.	Chlorids as NaCl in Urine, gm.	Phosphates as P_2O_5 in Urine, gm.
	January								
1	5- 6	Fat 1.5 per cent., carbohydrate 2.2 per cent.	3,862	630	1.009	Faint trace	1.46†	.895	.529
	6- 7	Protein 3.4 per cent.	4,076	490	.....	Negative	....	.608	.586
	7- 8		4,027	505	.....	Faint trace	....	.869	.539
2	8- 9	Fat 1.6 per cent., carbohydrate 2.3 per cent.	3,957	355*	.....	Faint trace	1.40†	.693	.354
	9-10	Protein 4.0 per cent.	4,102	570	.....	Faint trace	....	.775	.405
	10-11		4,090	500	.....	Faint trace	....	.770	.406
3	11-12	Fat 1.7 per cent., carbohydrate 2.0 per cent.	4,114	410	1.013	Considerable	1.35†	.872	.416
	12-13	Protein 4.6 per cent.	4,051	390	1.013	Considerable	....	.924	.371
	13-14		3,998	370	1.014	Considerable	....	1.314	.357
4	14-15	Fat 1.7 per cent., carbohydrate 2.1 per cent., protein 5.1 per cent.	3,948	340	.....	Considerable	1.19	.565	.346
5	15-16	Fat 1.8 per cent., carbohydrate 2.3 per cent.	3,961	295	1.019	Trace	1.27†	.541	.266
	16-17	Protein 5.5 per cent.	3,944	295	1.015	Faint trace	....	.506	.229
	17-18		3,914	400	1.019	Trace	....	.570	.467
6	18-19	Fat 1.5 per cent., carbohydrate 2.4 per cent.	4,034	420	1.019	Small trace	1.31†	.422	.449
	19-20	Protein 6.0 per cent.	4,059	280	1.021	Considerable	....	.689	.348
	20-21		4,093	440	1.021	Negative	....	1.142	.469
	21-22		4,026	250*	1.020	Considerable	....	.695	.318
7	22-23	Synthetic food, 1.8 per cent., carbohydrate 1.8 per cent.	4,045	490	1.016	5-10 per cent.	.579†	.450	.406
	23-24	Protein 5.9 per cent.	4,090	480	1.016	20-25 per cent.	....	.085	.535
	24-25		3,980	520	1.014	Small trace	....	0	.540
	25-26		4,026	490	1.018	10-15 per cent.	....	0	.572
	26-27		3,939	...	.....	.....	....	....	....

*Loss. †Average.

A BRIEF REPORT OF AN EPIDEMIC OF SORE THROAT WITH INVOLVEMENT OF THE CERVICAL LYMPH-NODES *

JOHN RUHRÄH, M.D.
BALTIMORE

There have been reported from time to time in European cities certain epidemics more or less associated with the milk-supply. Some of these epidemics have had a clinical picture which is more or less characteristic and which has been called by the English observers septic sore throat. The report of the United States Public Health Service records eight epidemics that occurred in England, the first in 1881 and the last in 1905. Bacteriologic examinations were not made in all these, but in the cases so studied the streptococcus was found. In seven of the eight epidemics one, or more, cows was discovered suffering from mastitis or from an eruption of the udder. In 1908 there was a remarkable epidemic which occurred at Christiania; this was found to be due to one milk-supply, and one cow was discovered with a diseased udder. From the cow there was isolated a streptococcus which was found in every way identical with the streptococci obtained from the patients suffering with the disease. The methods in use at that time for differentiating the varieties of streptococci were not as good as at present and even our present methods leave much to be desired.

Similar epidemics have been reported in other foreign cities. The first outbreak of this kind in the United States with which I am familiar occurred in Boston in 1911. This epidemic was one of unusual severity, affected chiefly adults, and was finally traced to one of the largest and best controlled dairies supplying milk in Boston. This year, in the month of February, a similar infection was noted and Dr. Mark Richardson, secretary of the Massachusetts State Board of Health, in a letter writes: "We found at a milk depot of this firm conditions which we thought explained it. At any rate we requested that all the milk from this special milk depot be pasteurized, and the epidemic promptly ceased."

A similar outbreak occurred at Concord, N. H., and Davis and Rosenow reported a large number of cases that occurred in Chicago.

In Baltimore the epidemic began early in January. Curiously enough, one or two cases presenting exactly the same clinical picture were

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*Read at the meeting of the American Pediatric Society, Hot Springs, Va., May, 1912.

observed in December. The cases increased throughout February and in the third and fourth weeks became very numerous. After the first three weeks of March were over very few of the typical cases were noted, although there was a large number of cases of sore throat from which streptococci could easily be isolated, but which were free from the complications that characterized the epidemic.

Dr. Louis Hamburger was one of the first to recognize the epidemic as milk-borne, and the subject of the disease was talked over at a meeting called at his suggestion. The results of his experiences were charted and they showed conclusively that a great number of people were using milk from one of the largest dairies in the city. For example, in two homes for trained nurses one used milk from the suspected dairy and showed a percentage of 71.4 of the inmates suffering during the epidemic from some form of sore throat; this is in striking contrast with 8.3 per cent. in the other home which was using milk from another dairy. In sixteen fatal cases it was found that fourteen used milk from the suspected dairy, and that in two the milk-supply was unknown. Both of these unknown cases occurred in adults, one before the milk-supply was suspected, and the other was in a hospital patient who was too ill to be interrogated.

Another method of studying the relation of the disease to the milk-supply was by taking a group of households using the infected milk and a similar group, taken at random, using other milk, the only requirement in the cases so taken being that the households should contain two or more children. The results were about the same as that shown in the nurses' homes.

Subsequently the disease was studied by Dr. Frost of the United States Public Health Service, and the results of his investigations will be published in a separate paper. He found, however, that in about 80 per cent. of the cases which occurred from the middle of February to the middle of March the patients were using milk from a suspected dairy. He was able to find some 600 undoubted cases of the disease, but this represented only about one-third or one-fourth, or even a smaller percentage, of the actual number of cases which occurred during the epidemic. In these 600 odd cases there were twenty-eight fatalities and twenty-two of these had used milk from the suspected dairy.

An interesting point in relation to the suspected dairy in the Baltimore epidemic was that previous to the epidemic the flash method of pasteurization had been used. Wishing to make some repairs and improvements in the pasteurizing room, pasteurization was stopped during a considerable portion of the time in January and February and in the first part of March. The weather during this time was extremely cold and it was thought that the repairs and improvements could be made more safely at this time than at any other season of the year. Following

the announcement that the epidemic was caused by milk a holding pasteurizer was installed and after this the epidemic promptly ceased. About this time, however, it should be borne in mind that the public was repeatedly warned through the daily papers to boil the milk, and a very large number of people using milk followed this direction and this undoubtedly had much to do with the prompt cessation of the epidemic.

The Baltimore epidemic differed somewhat from the others which have been described, in that children were very largely affected, fully 50 per cent. of the cases occurring in early childhood. Cases were noted in children as young as 4 months, and Dr. Hamburger had one case at 65 years of age, and he also stated that he knew of one case, which was not included in his series of cases, in which the patient was 86 years of age. In my own cases, all in children, almost all of them occurred between the ages of 12 and 24 months.

There seems to be little doubt that the disease was originally derived from using contaminated milk, but once having been started it was possible to have the disease transmitted in the ordinary ways. It frequently happened that all the members of a household would be affected, but for the most part the adults escaped with light attacks. In a number of instances nurses in constant attendance on the children became affected and had typical attacks. In one instance a cat which drank freely from the infected milk was affected very much in the same way that children were, that is, with an angina and enlargement of the cervical lymph-nodes.

Bacteriology.—I am indebted to Dr. Standish McCleary for the following information: The organism, frequently in pure cultures, which was seen in smears made from these patients, was a diplococcus with a distinct capsule, easily demonstrable with the usual capsular strains. The diplococcus was Gram-positive. When grown on all mediums this capsule disappears but returns after passage through mice. When cultivated the organism takes the form of a streptococcus in short chains in which the diplococcus arrangement is preserved. Occasionally tetrads are seen. On slant agar a thin, slightly moist dewlike colony is obtained. Hemolysis occurs on blood-agar. Litmus milk is acidulated and coagulated and broth is rendered turbid. Lactose and saccharose are fermented but not inulin. The thermal death point in milk is 54 C. at an exposure of twenty minutes. The organism is found in the pus of the otitis which occurred so frequently, and also in the suppurating lymph-nodes, which were not frequent. In some cases the pneumococcus was obtained from the throat, sometimes in pure culture.

The Clinical History.—There are four classes of cases met with—mild cases, cases of average severity, severe cases, and cases of unusual intensity, usually owing to some severe complication occurring at the onset.

The mild cases were for the most part in adults and many were not sufficiently ill to go to bed; very few of these came under my personal observation. They were characterized by an angina of mild intensity, and for a day or two slight enlargement of the cervical lymph-nodes. There was slight fever, headache and general malaise. These symptoms persisted for several days and then usually from two to three weeks would elapse before the patient felt quite well, and many complained of slight recurrence of the symptoms, lasting twenty-four hours or more. There were some mild cases in children; by far the greatest number, however, presented the same clinical picture. There was sudden onset with fever, and occasionally a convulsion; the temperature varied from 101 to 104 or 105 F., and there was considerable prostration. At the outset the only physical sign of any importance was the general redness of the pharynx and pillars of the fauces; this was usually a dusky red and at some places there were slight patches of exudation, particularly on the tonsils. This exudation could easily be mistaken for diphtheria but was not nearly so adherent, and much of it consisted of pus which could easily be wiped off. In other cases there was the typical appearance of a tonsillitis, the crypts being filled with a more or less hard and purulent material. Children old enough complained of pain usually located in the head, neck or abdomen. After two or three days there was marked swelling of the lymph-nodes at the angle of the jaw. These were almost always on both sides and varied in size from a hazel nut to a pigeon's egg, or even larger. There was more or less exudate into the subcutaneous tissues, and these swellings were painful and tender to the touch; they persisted for two or three weeks and gradually subsided, in most instances leaving the nodes normal in size or very slightly enlarged. The fever and prostration varied greatly, the mild cases lasting a week to ten days; some of the more severe cases continued as long as two weeks, and sometimes longer.

The severe cases came on with great intensity, usually either with a chill, or more commonly with a convulsion, the temperature rising rapidly to 106 or 107 F., and sometimes even higher. The appearance of these children was very alarming, the pulse was rapid and weak and the respirations irregular and shallow. There were marked pallor and more or less cyanosis; in some there were marked vomiting and sometimes diarrhea. After a day or two the lymph-nodes at the angle of the jaw enlarged and usually this was coexistent with an improvement in the general condition. In many of the severe cases there were complications as noted below.

The worst class of cases either started with very severe symptoms or sometimes these symptoms came on two or three days later. In these cases there was no enlargement of the lymph-nodes, or the enlargement

was slight, and the general clinical picture was that of a septicemia with very high, irregular temperature, great prostration, usually numerous complications and death. Certain other cases were characterized by the appearance of a peritonitis which was apparently only a complication in the course of the septicemia. The fatal cases are striking, the usual history being of a child in perfect health taken with a convulsion and high fever and slight redness of the throat; the child was either comatose or partially so; there were generally vomiting and diarrhea and distention of the abdomen, which later became very tender, and then a considerable rigidity of the muscles developed; within forty-eight or seventy-two hours after the onset the child would die, sometimes from failure of respiration, occasionally from failure of the heart.

Complications.—The complications attending this disease were remarkable for their number and their intensity; most common of all was the inflammation of the middle ear, which occurred in from 30 to 40 per cent. of the cases. Next to this were irregular swellings, sometimes suggesting an edema, at other times suggesting abscess formation, although these swellings rarely suppurated. The swellings were most frequently noted about the throat over the epiglottis, or at the base of the tongue at the side, sometimes in the floor of the mouth, sometimes posteriorly in the pharynx, suggesting retropharyngeal abscess. Suppuration was not a very common thing in my experience, apart from the inflammation of the middle ear, and in only two instances did the lymph-nodes in the neck suppurate, and in one of these the suppuration evidently followed a retrotonsillar abscess. In one instance there was a retropharyngeal abscess, and in one other case numerous points of suppuration occurred apparently independent of the swollen nodes. Edema of the eyes, affecting both lids and the tissues about the orbit, was not uncommon, and this usually, although not always, was unilateral and accompanied with nothing more than a slight conjunctivitis with little or no discharge. Bronchitis was not uncommon, and quite a number of patients had pneumonia as a complication. Gastro-intestinal disturbances were also common, usually consisting of vomiting and a very irritable stomach, and later on a more or less intense diarrhea. In three cases there was an erysipelas, two occurring on the scalp and one on the face. These ran a typical erysipelas course and finally stopped suddenly. In some cases the joints were swollen, and in some others the tissues about the joints, the joints themselves remaining more or less free. In some cases there were petechiæ, and in others larger ecchymotic spots, and in one instance there occurred about the tenth day very large subcutaneous hemorrhages, as if there had been an actual rupture of some of the larger vessels and which suggested the rupture of the vessels which has been noted in experimental work in pneumococcus infections. In one instance the hemor-

rhages occupied both sides of the scalp, and also the arm from the wrist nearly to the shoulder, the swelling thus produced being larger than one would imagine was possible.

CONCLUSIONS

The lessons to be learned from this epidemic are as follows:

1. A streptococcus infection may be caused by infected milk, and this disease may be exceedingly severe and attended with numerous complications and fatalities.

2. Even in cold weather milk may be the source of the disease.

3. No matter how carefully raw milk is handled it may at times be a source of danger.

4. The milk supplied to cities should be pasteurized, and where by accident the dairy company cannot properly pasteurize its milk, it should be compelled to notify its consumers, so that they can either pasteurize or boil the milk.

EFFECTS OF COLD AIR ON BLOOD-PRESSURES OF CHILDREN AND YOUNG ADULTS IN VARIOUS STAGES OF TUBERCULOSIS *

B. RAYMOND HOOBLER, A.M., M.D.
NEW YORK

Through the work of many observers it has been definitely established as a clinical fact that the blood-pressure of patients with tuberculosis is reduced considerably below normal. Most of the observations on record, however, have been made on adults and but few on children. Strandgaard's[1] reports included a large number of children, but his figures were not given separately. Pottenger's[2] series included only four patients between 14 and 16 years, all of whom showed lower pressure than normal. Levy's[3] cases reported but two children in very early stages, both of whom showed no change from normal. A large number of cases have been reported in which the ages of the children have not been given. There are, however, sufficient reports to show that the pressures of children are affected much as those of adults. Emerson[4] has recently presented an exhaustive study and reviewed the various theories of causation of this hypotension. He concluded that "the causes of low blood-pressure in tuberculosis are probably, primarily, a toxic action on the vasomotor center in the medulla, allowing of a vasoparesis or stimulating an active vasodilatation, and secondarily, progressive cardiac atrophy or degeneration." It is evident, therefore, that in a disease in which the blood-pressure is so constantly lowered, one of the essential principles of treatment should be the combating of this lowered pressure.

Dec. 15, 1910, I presented to the medical section of the New York Academy of Medicine a preliminary report with charts, showing the effect of cold air on the blood-pressure of a young adult having incipient tuberculosis, an abstract of which appeared in *The Medical Record*, Jan. 28, 1911.

Since that time a series of blood-pressure observations, 150 in all, have been made on children and young adults in various stages of pulmonary tuberculosis. In general it may be stated that every case having

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*Read in the Section on Diseases of Children of the American Medical Association at the Sixty-Third Annual Session held at Atlantic City, June, 1912.

1. Strandgaard: N. J. Hosp.-Tid., 1907, xv, 1041.
2. Pottenger: Arch. Int. Med., 1909, vi.
3. Levy: Beitr. z. klin. d. Tuberk., 1905, xiv, 99.
4. Emerson: Arch. Int. Med., 1911, vii, 441.

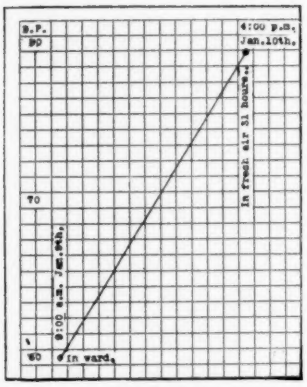

Chart 1

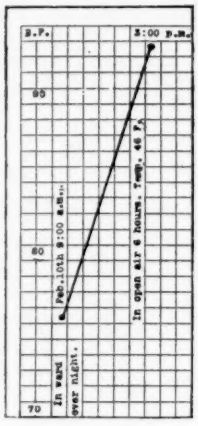

Chart 2

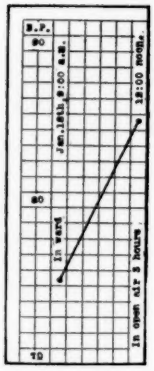

Chart 3

Chart 1.—Advanced case pulmonary tuberculosis. Girl aged 1 year. Febrile throughout entire illness. Died forty-five days after this observation. Chart shows exceedingly low pressure when in ward, with a rise of 20 mm. Hg after being in cold air for thirty-one hours.

Chart 2.—Advanced case of pulmonary tuberculosis. Boy of 1 year; admitted January 27, died February 13. Observations taken three days before death.

Chart 3.—Moderately advanced case pulmonary tuberculosis. J. F., boy, aged 2½ years. On day observations were made the child had a temperature varying from 100 to 102.5 F. The child was discharged improved after two months in the hospital. Chart shows a rise of 14 mm. Hg after being in cold air for three hours.

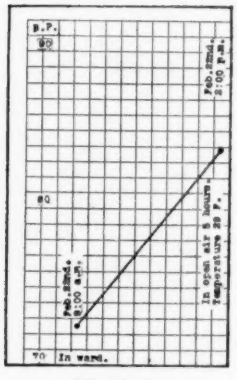

Chart 4

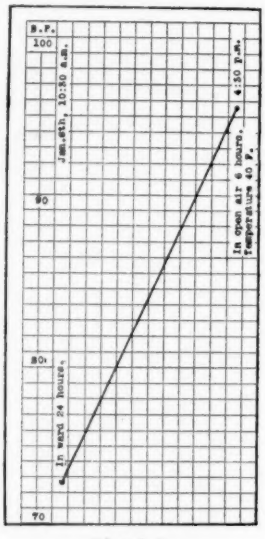

Chart 5

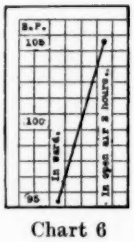

Chart 6

Chart 4.—Moderately advanced case of pulmonary tuberculosis. Girl of 3 years. Febrile throughout course; not improving.

Chart 5.—Incipient case of pulmonary tuberculosis. R. G., boy, aged 5 years; slight involvement at right apex; temperature below 100 F. Discharged improved 17 days after observations were taken.

Chart 6.—Incipient pulmonary tuberculosis. M. C. young adult, aged 16 years; slight involvement at right apex. Temperature below 101 F. Sent to mountains two days after observation. Chart shows a rise of 16 mm. Hg after being in the open air for two hours.

a definite pulmonary lesion showed a decrease in blood-pressure. When transferred from the ward or small room to the open air these patients all showed an increase in blood-pressure. This explains, to a large degree, the value of the outdoor treatment of tuberculosis and gives a very definite basis on which to urge this form of treatment.

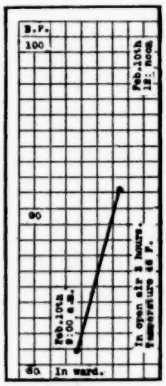

Chart 7

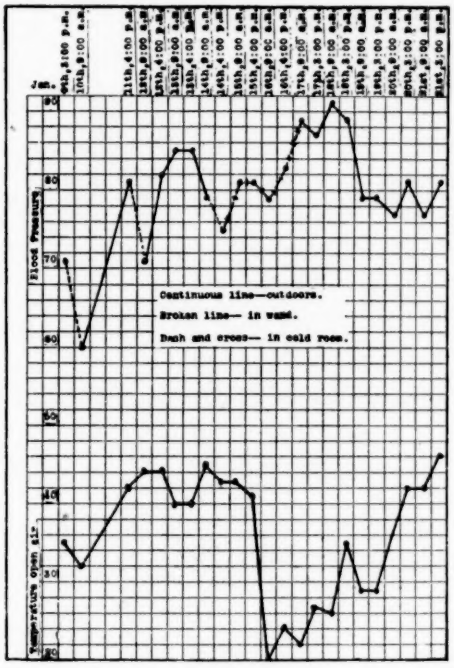

Chart 8

Chart 7.—No demonstrable lesion; von Pirquet reaction, positive. D. W., girl aged 2 years. Clinical diagnosis, rachitis; no demonstrable sign of tuberculosis. Chart shows but a slight rise in pressure when put in the open air.

Chart 8.—Advanced case of pulmonary tuberculosis. Girl 1 year old was kept constantly under influence of cold air either in a cold room or out of doors for period of sixteen days, except on three very unpleasant days. Both blood-pressure and out door temperature are shown on the chart. It should be noted that the blood-pressure when in the ward varied from 60 to 70 mm. Hg and that through the influence of continuous residence in the cold air the pressure was maintained at an average of 80 mm. Hg, being about the normal pressure for a child of 1 year. It should be further noted that in periods of lowest temperature the blood-pressure rose the highest. It should also be noted that after several days in the open air when the child was brought into the ward the blood-pressure did not fall to as low a point or as much as before fresh cold air treatment was begun.

The charts presented are cases of advanced, moderately advanced and incipient pulmonary tuberculosis, also one which gave a possitive von Pirquet reaction, but which had no demonstrable pulmonary lesion. (The charts with their legends are sufficiently clear to need no further discussion.)

SUMMARY

From a study of the foregoing charts it appears that:

1. Blood-pressure in children having tuberculosis is persistently low, as has been found to be the case in adults.

2. When a patient is transferred to the open air there is a gradual increase of blood-pressure within one or two hours.

3. If the patient is kept constantly in the open air the pressure is raised to well within the normal limits and sustained at that point as long as the patient remains in the open air.

4. The more advanced the case, the lower the pressure indoors, and the higher the rise when put in the open air.

5. After several days in the open air the blood-pressure does not fall as much when placed in ward as it did previous to outdoor treatment.

131 East 67th Street.

PAROXYSMAL HEMOGLOBINURIA*

REPORT OF A CASE IN A FEMALE CHILD; POSITIVE WASSERMANN IN CHILD AND MOTHER

LOUIS C. AGER, M.D.
BROOKLYN

Charpentier's treatise on the various types of hemoglobinuria is so concise and reviews the literature so thoroughly to the date of its publication that it would be futile to go over the details here. He describes paroxysmal hemoglobinuria as follows:

It usually attacks men (women are seldom affected) of a pale and sallow complexion, who may or may not have had some specific disease, such as malaria or syphilis, or who have a bad family history, in fact, whose vitality is from any cause lowered.

After exposure to cold the patient has rigors and feels ill. Soon after he passes dark colored urine which contains large quantities of hemoglobin but rarely blood corpuscles.

Holt says in the last edition of his book, page 602:

Paroxysmal hemoglobinuria occurs in childhood, although it is an extremely rare condition.

The subject is not mentioned in other American text-books on children's diseases. Pfaundler and Schlossman describe the disease but do not give the latest studies in regard to it.

Following Ehrlich's theories, Kretz and Eason in 1902, and Donath and Landsteiner in 1904, studied the blood of these patients and demonstrated the following:

First, that the blood-serum contains a complex hemolysin of amboceptor — complement nature.

Second, that this lysin can only act in the presence of this complement, that is, the serum may be rendered inactive by moderate heat and then reactivated by the addition of a small amount of some other serum which in itself is not hemolytic.

Third, this lysin must be chilled far below normal body temperature in order to become active, either in the body or in the test tube.

Fourth, this lysin is both autohemolytic and isohemolytic; that is, it destroys the red cells of the individual and also the red cells of other individuals of the same species.

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*Read before the Medical Society of the County of Kings, N. Y., June 18, 1912.

Although syphilis has always been assigned as one of the principal causes of this symptom-complex, it is only since the general application of the Wassermann reaction that any accurate figures have been obtained. During the past two years I find records of thirty-four cases; in addition, R. A. Cooke reported a case in May at the Academy of Medicine, as yet unpublished. The case here reported seems to be the thirty-sixth. Some of the facts are as follows:

Reference	Age	Sex	Syphilis At Age of, Years,	First Attack of Hemoglobinuria, At Age of, Yrs.
.....	...	...	...	...
1.	64	M	48	60
2.	28	M	22	25
3.	48	M	Was	..
4.	48	M	?	40
5.	36	M	25	29
6	34	M	24	33
6.	33	F	Was	33
7.	8	F	Congenital	5
7.	7	M	Congenital	5
7.	32	M	Congenital	24
8.	10	..	Congenital	5
9.	56	M	30	55
10.	4	M	Congenital	4
11.	30	F	?	25
12.	16	M	Congenital	..
12.	37	M	Acquired	..
12.	45	M	Acquired	..
12.	53	M	Acquired	..
12.	42	M	Acquired	..
12.	50	F	Acquired	..
12.	27	M	Acquired	..
12.	49	M	Acquired	..
12.	24	M	Acquired	..
12	14	M	Congenital	..
12.	15	M	Congenital	..
12.	18	F	Congenital	..
12	19	F	Congenital	..
12.	7	M	Congenital	..
12.	42	M	Congenital	..
12.	27	M	Acquired	..
12.	6	M	Congenital	..
12.	6	F	Congenital	..
12.	20	M	Congenital	..
12.	30	M	Acquired	..
14.	38	M	Congenital	20
15.	3	F	Congenital	2

These figures confirm the observation of the earlier writers that a large majority of the patients are males; in this series 27 males, 8 females, 1 unknown.

In the different age periods we find 23 cases over 20 years, 4 cases between 15 and 20 years, and 9 cases under 15 years. At first sight these facts seem to agree with Charpentier's statement that this is chiefly a disease of adults. As a matter of fact, however, the statistics are about what would be expected under the law of averages. That is, one-quarter of the cases are in early life as a late manifestation of congenital lues, one-eighth during adolescence and the others in adult life.

Of the total 30 cases, 17 had congenital syphilis, 15 acquired syphilis, 2 had positive Wassermann tests, type unknown, and in 2 the question of syphilis was not determined. This seems to indicate that hemoglobinuria is much more apt to follow congenital than acquired syphilis, but I have no accurate knowledge in regard to the relative frequency of the two types.

CASE REPORT

The case I desire to report is the following:

History.—L. C., female, aged 3 years and 4 months, a Syrian child born in Syria, was first seen, April 1, 1912. Both parents are living and apparently in good health. The mother is rather fat and was in the last month of pregnancy when first seen. The father is a thin nervous man with the typical Syrian physiognomy. The Wassermann test was negative. The mother was previously married and had two miscarriages. Her first husband died of "heart disease." There has also been one miscarriage since this child was born. There was positive Wassermann reaction. During the first week in May the mother gave birth to an apparently healthy boy, fat, skin healthy, no snuffles. At 2 weeks the baby had a slight cold in the head and diarrhea. It began to lose weight and had some desquamation on its hands and feet. At present—June 5, 1912—he has an enlarged liver, profound jaundice, bile in the urine and is failing rapidly, in spite of the use of calomel and mercuric chlorid. June 3 a Wassermann test was made but neither the test nor the control showed cytolysis, possibly on account of the large amount of bile in the blood serum.

The patient has always been well, according to the mother: that is, she has had no acute diseases. She was nursed for the usual period and developed normally during the first year although she had some diarrhea. She has always had a good appetite and is apt to be constipated. At 1 year and 10 months she had the first attack of "bloody urine" and has had them at varying intervals ever since, particularly during cold weather. The attacks come on after exposure to cold and are ushered in by definite chills—a very rare symptom in small children. The chill is followed by pain in the back, marked prostration and drowsiness and then the "bloody urine," without any bladder irritability.

Physical Examination.—The child has the typical Syrian features, is short and stocky, a fat little girl. She is very anemic and has some marginal blepharitis. There is very little evidence of rachitis although 80 per cent. of the Syrian children in this country seem to be markedly rachitic. Apparently the child is otherwise normal. There is no pain nor tenderness.

The history indicated some chronic infection in the urinary tract—tuberculous kidney—stone in the kidney—colon pyelonephritis. The fact that she was first attacked in Syria suggested the possibility of a bilharzia infection. Urotropin and water were prescribed and a sample of urine was requested. On the way home from my office she had another chill and in two hours I had a sample of dark red urine without any blood cells, which showed that it was not hematuria but hemoglobinuria. This was confirmed by a spectroscopic examination. A few hours later the urine was clear, with only a trace of albumin The child was

placed in the Long Island College Hospital for greater convenience and Drs. Avery, White and Murray of the Hoagland Laboratory very kindly undertook the examination of the blood, and I am indebted to them for the chief interest of this paper. During the few days between the visit to my office and admission to the hospital the child had a number of attacks and the anemia was profound. Dr. Murray found the blood condition as follows:

Hemoglobin	45%
White cells	5,200
Red cells	3,200,000
Color index	0.7
Differential count:	
Polynuclears	35.4%
Lymphocytes	51.0%
Large mono. and transitionals	12.8%
Eosinophils	0.8%

One neutrophilic myelocyte. No erythroblasts.

There was marked megalocytosis and polychromatophilia and moderate poikilocytosis. The Wassermann test was positive.

This indicated not only a profound anemia but also a marked degenerative condition of the red cells and an exhaustion of the organs of red cell production. Nevertheless the confinement in bed and the even temperature in the hospital promptly checked the cytolysis, and improvement was rapid. She was removed by the family at the end of two weeks and soon after developed German measles. In spite of this there were no more attacks, probably on account of the season of the year. May 29 the blood-examination was as follows:

Hemoglobin	70%
Red cells	4,200,000
White cells	8,400
Polynuclears	30.0%
Lymphocytes	55.0%
Eosinophils	1.8%
Large mononuclears	0.0%

Red cells normal in shape, size and staining.

EXPERIMENTS IN HEMOLYSIS

The first attempt to get enough blood for hemolysis studies was not very satisfactory on account of the adipose tissue and the small size of the veins. Later I opened a vein in the foot and secured 10 c.c. With this serum a number of tests were made in which the results coincided with the reports of other observers. The two experiments demonstrating hemolysis were as follows:

The blood was allowed to clot and the clear serum was drawn off. Some of the red cells were then washed out of the clot and a 5 per cent. volumetric suspension of them was made in normal salt solution. In each of two test-tubes were put .25 c.c. of the serum and the same amount of the suspension of red cells. One of these tubes was packed in ice for half an hour, and then both were placed in the incubator at 37 C. for two hours. In the tube that had been chilled the red cells were completely destroyed; in the other tube they were not affected.

The second experiment was the same as the first except that the red cells were derived from a normal human being. Hemolysis was the same as in the first experiment. This second experiment shows that the old idea that the red cells in these patients are so diseased that they break down easily, is a mistake. It proves that the blood-serum contains some substance which unites with the red cells when the blood is sufficiently cooled, as in the superficial capillaries, and that the cells are then dissolved when they are again warmed in the interior circulation.

That there are two steps in the chemical process is shown by "inactivating" the serum by a temperature of 50 C. for twenty minutes; after which it will not destroy the red cells. If, however, a small amount of normal serum is added — which in itself has no cytolytic power — the hemolysis again occurs under the same conditions as before. In this particular case it was found that the serum became inactive after standing at room temperature for twenty-four hours, but it was readily reactivated by the addition of complement in the form of normal serum.

As this is merely a clinical report I will not take up the discussion of the many interesting biochemical problems involved. Many of them have been studied by Moss, Kumagai and Cooke, and others have not yet been investigated. The following are a few of the questions that might be studied:

Are there two hemolysins present — an autohemolysin and an isohemolysin?

If so, can they be separated? How do they differ?

Can both be entirely removed from the serum by absorption by red cells?

If so, will the remaining serum give a positive Wassermann reaction?

To what extent, if any, can the steps in the process be reversed?

What relation does this process of hemolysis bear to artificially induced hemolysis?

The chief points of clinical interest in this report are the sex of the patient, her present age of 3¼ years and the fact that the first attack occurred during the second year of life. This is I believe the youngest recorded case.

ADDENDUM

The infant brother referred to in the report died June 14, 1912. Necropsy revealed that the liver was very dark in color, moderately enlarged and somewhat friable. No spirochetes were found, and none of the internal organs showed definite evidences of syphilis.

137 Clinton Street.

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11. Goodall: Jour. Am. Med. Assn. 1910, liv, 1372.
12. Kumagai and Jnoue: Deutsch. med. Wchnschr., 1912, No. 8, 361.
13. Charpentier: Hemoglobinuria. Balliere, Tindall & Co., London, 1910.
14. Cooke, R. A.: Not yet published.
15. Case here reported.

ON THE MODE OF INFECTION IN EPIDEMIC CEREBRO-SPINAL MENINGITIS *

DAVID BOVAIRD, JR., M.D.
NEW YORK

The *Diplocuccus intracellularis* was identified as the specific excitant of epidemic cerebrospinal meningitis by Weichselbaum in 1887. The procedure of lumbar puncture as a means of obtaining cerebrospinal fluid and attaining an etiologic diagnosis in cases of meningitis was introduced by Quincke in 1891.

The studies of meningitis made possible by this means have established beyond question the relationship of the meningococcus to the epidemic type of meningitis which has presented itself in various parts of the world during the last decade. As this relationship has been made clear, the problem of the control of this dreaded disease has focused itself about the life of the specific organism, its distribution in the body of those affected by the disease, its paths of exit from the body, its viability, and the mode by which the infection might be conveyed to others. Most of the points of interest and importance in these relations have been quite thoroughly cleared up.

The meningococcus has been found not only in the cerebrospinal fluid of those suffering from the disease but in the conjunctiva and the eye, in the nose and throat, in the pleura and lungs, in the pus of joints, in the throat, and in the blood. So far as our present knowledge leads us, the organism may be excreted from the body by the purulent discharges from an active conjunctivitis or by the secretions of the nose, throat and bronchi. While the organism has been found in the conjunctival secretions by Koplik,[1] Robinson,[2] and others, and the possibility of contagion from that source must be recognized, active conjunctivitis is not a frequent accompaniment of the disease and infection from that source must be rare.

In like manner, as Jakobitz[3] has shown, the meningococcus may be found in the lungs both in those suffering from cerebrospinal meningitis, with or without definite pulmonary complications, and in rare instances in pneumonias and bronchial catarrhs occurring independently of meningitis.

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*Read at the meeting of the American Pediatric Society, Hot Springs, Va., May, 1912.

1. Koplik: Osler's Mod. Med., ii, 499.
2. Robinson: Am. Jour. Med. Sc., 1906, cxxxi, 603.
3. Jakobitz: Ztschr. f. Hyg. u. Infections-krankh., 1907, lvi, 175.

The greatest interest and importance, however, attach to the presence of the meningococcus in the nose and throat, because its presence in these passages may not only be a ready means of disseminating the organism outside the body of the patient, but also suggests the possibility of direct infection of the meninges from this source.

Since von Lingelsheim directed attention to the fact that the organism was to be sought not in the nares but in the nasopharynx, the reports of its discovery in cases of meningitis have shown increasing positive results. With the question of the identification of the *Diplococcus intracellularis* we need not here concern ourselves. The work of Councilman, Mallory and Wright,[4] Albrecht and Ghon,[5] and von Bettencourt and Franca[6] has made the differentiation of the meningococcus so certain that reports conforming to the established standards can be accepted as reliable.

From reports of the occasional finding of the specific organism in the nasal or nasopharyngeal secretions, we find more and more positive results recorded. Thus Goodwin and von Scholly[7] obtained positive results from the nasal mucus of twenty-seven out of fifty-two (50 per cent., plus) cases examined during the first two weeks of the disease and Dieudonné four positive findings in six cases (67 per cent.) and von Linglesheim[9] under favorable conditions forty-six positive results in forty-nine examinations (93.8 per cent.). It seems probable that the organism is present in the nose or nasopharynx of most of the cases of epidemic meningitis during the early stages of the disease.

But it has also been found in the same site in well persons, especially in those who have been in contact with cases of meningitis and also in many in whom no knowledge of exposure can be obtained. Thus Goodwin and von Scholly found the specific organism in the nasal secretions of 10 per cent. of forty-five "contacts;" Dieudonné obtained five positive results in thirty-nine trials, and Fraser and Comrie[10] ten in sixty-nine trials, of contacts.

In the effort to control the inroads of the disease in the German army, similar investigations have been made on a large scale in regiments exposed to the disease, with most interesting results. Hübener and Kutscher[11] report that in 400 men of one batallion they found eight

4. Councilman, Mallory and Wright: Epidemic Cerebrospinal Meningitis, Rep. Mass. St. Bd. Health, Boston, 1898

5. Albrecht and Ghon: Wein. klin. Wchnschr., 1901, xiv, 984.

6. Von Bettencourt and Franca: Ztschr. f. Hyg. u. Infections-krankh., 1904, xlvi, 463.

7. Goodwin and von Scholly: Jour. Infect. Dis., 1906, p. 21.

8. Dieudonné: Centralbl. f. Bakteriol., 1906, xli, Pt. 1, 418.

9. Von Linglesheim: Klin. Jahrb., 1906, xv, 400.

10. Fraser and Comrie: Scottish Med. and Surg. Jour., 1907, xxi, 18.

11. Hübener and Kutscher: Deutsch. militär-arzt. Ztschr., 1907, xxxvi, 639.

coccus carriers although there were no cases of meningitis in the regiment itself at the time, and Vagedes[12] in 1,703 men examined under like conditions found ten carriers.

Under ordinary conditions the meningococcus quickly perishes outside the human body. It therefore seems highly probable that the spread of the disease depends on the presence of the specific organism in the nasal passages or respiratory tract of those sick with the disease and also of many persons in good health. The respiratory tract, and especially the nasopharynx, appears to be the usual portal of entry.

These facts being accepted, how does the organism from the nasopharynx or other part of the respiratory tract reach the meninges and there set up its specific inflammation?

The proximity of the nasopharynx to the meninges naturally suggested the possibility of direct infection. Of many contributions to the discussion of this subject, that of Westenhoeffer[13] is based on the study of the most ample material and is of most interest.

As the results of his anatomic observations, Westenhoeffer lays emphasis on the following facts:

1. The meningitis begins at the base of the brain, in the region of the optic chiasm and about the hypophysis cerebri, and from this point spreads in all directions.

2. There is a suppurative exudate about the gasserian ganglion and in the sheaths of the several motor nerves of the eye.

3. Constant redness, swelling and hypersecretion of the nasopharyngeal tonsil and adjacent parts with an ascending otitis media.

4. The sphenoidal sinuses are constantly affected in all patients over 3 years of age. They were found markedly affected in twelve out of thirteen cases.

5. The antrum of Highmore is less often involved.

6. The ethmoidal sinuses are rarely and but slightly affected.

7. In all cases there is some swelling of the cervical lymph-nodes.

From these observations it seemed probable that there might be direct infection of the meninges from this nasopharyngeal focus through the sphenoidal sinuses. Especial emphasis is laid on the perihypophysial inflammation because of the close relation of the hypophysis to the sphenoidal sinuses and the known fact that in fetal life the sella turcica communicates with the throat through a hypophysial passage.

Two lymphatic paths are open for infection of the meninges from the nasopharyngeal process.

1. The infectious agent may make its way along the nerve sheaths, especially the several branches of the gasserian ganglion, as staphylococci,

12. Vagedes: Deutsch. militär-arzt. Ztschr., 1907, xxxvi, 647.
13. Westenhoeffer: Klin. Jahrb., 1906, xv, 657.

streptococci and typhoid bacilli have been shown by Homen to rise along the lymph channels of the sciatic nerve to the spinal cord. The inflammatory deposits surrounding these nerves are, however, readily shown to be secondary to the meningitis and descending, not ascending, processes.

2. The path of invasion may be along the carotid sheath to the region of the hypophysis.

However, investigation shows that the same perihypophysial inflammation is found in both otitic and tubercular meningitis. In the latter at least of these the infection undoubtedly reaches the meninges through the blood-stream and not by lymphatic channels. The value of the perihypophysial inflammation as evidence of the lymphatic transmission of the infection is therefore slight.

In the end Westenhoeffer admits the impossibility of proving the lymphatic transmission and assumes that the infection must reach the meninges through the blood-stream.

He even suggests that the whole throat affection may be secondary, although this seems improbable, inasmuch as it appears too early, in some cases before the onset of the meningitis, and also because the specific organisms are known to be often found in the throats of persons in good health (carriers).

Lymphatic transmission having apparently failed of proof, Westenhoeffer regards the infection as carried by the blood and probably by the arteries, inasmuch as no extensive thromboses are regularly present in cerebrospinal meningitis.

The cocci, as he says, are known frequently to be found in the blood, in some cases in the earliest stages of meningitis. In two or three cases lasting less than twenty-four hours, an endocarditis of the mitral valve and purulent myocarditis produced by the meningococci have been found.

Göppert[14] similarly summarizes his study of this question in these words:

> The whole respiratory tract, from the nose to the pulmonary alveoli, shows in the early stages of epidemic cerebrospinal meningitis more or less severe inflammatory changes. These may precede the onset. Chance brings one or the other—the pharyngitis, tonsillitis, pneumonia or bronchial catarrh, otitis media—of these conditions into the foreground. None of these affections is obligatory and therefore the opinion may be advanced that sometimes this, sometimes that point of the respiratory mucous membrane becomes the portal of entry of the meningococcus. Therewith must we accept the fact that the meningococcus may reach the brain through the blood channels, a conception which obtains support from the presence of the meningococcus in the blood.

Thus these two observers, disagreeing at the outset as to the importance of the local lesions of the respiratory tract, come in the end to agreement as to the probable route of infection of the meninges.

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14. Göppert: Klin. Jahrb., 1906, xv, 527.

At this point the problem of demonstrating a meningococcus septicemia, either as an attendant feature of epidemic cerebrospinal meningitis or independently of it, becomes of great interest.

That the meningococcus may be found in the blood in certain cases of epidemic meningitis has been known for some time. Gwyn[15] first reported such a finding in a patient of Osler, and since then similar observations have been made by many others, Cochez and Lemaire,[16] Jakobitz,[17] Martini and Rohde,[18] Lenhartz,[19] Marcovitz,[20] Robinson[21] and Duval.[22] Elser,[23] in forty-one cases found the coccus in the blood in 10.25 per cent.; Dieudonné reports positive blood findings in four out of five cases, in one of which the nasal secretion was negative.

Especial interest, however, attaches to the presence of the meningococcus in the blood in patients free from meningitis. In 1908 I[24] reported the case of a girl of 15 years who presented some of the symptoms of cerebrospinal meningitis, but whose spinal fluid remained free from meningococci, while the organisms were found in the blood. At that time I was able to find in the literature three other reports of meningococcus septicemia without meningitis, these being recorded by Salomon,[25] Liebermeister[26] and Andrewes.[27] Netter has since recorded the case of a woman suffering from diarrhea, fever and general malaise, whose blood agglutinated two strains of meningococci, but whose blood culture was not taken. The patient's sister had cerebrospinal meningitis at the time.

Cecil and Soper[28] have collected from literature four cases of meningococcus endocarditis, two of these being the cases of Westenhoeffer already referred to, and add an observation of their own. The patients of Warfield and Walker[29] and Cecil and Soper gave no evidences of meningitis.

The occurrence of meningococcus septicemia both in conjunction with the cerebrospinal meningitis and independently of it, lends support to the view that the infection of the meninges is brought about through the blood, the primary focus being in the respiratory tract.

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15. Gwyn: Bull. Johns Hopkins Hosp., 1899, x, 112.
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21. Robinson: Bull Ayer Clin. Lab., 1903, i-iii, 27.
22. Duval: Jour. Med. Research, 1908, xix, N. S. xiv, 258.
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26. Liebermeister: München. med. Wchnschr., 1908, lv, 1978.
27. Andrewes: Lancet, Lond., 1906, lxxxiv-ii, 1172.
28. Cecil and Soper: Arch. Int. Med., 1911, viii, 1.
29. Warfield and Walker: Bull. Ayer Clin. Lab., 1903-6, i-iii, 81.

Elser and Huntoon[30] summarize the evidence of hematogenous infection in these words:

> **The early appearance of the meningococcus in the blood in a considerable number of cases, the appearance of general sepsis suggested by some patients early in the disease, the lesions in parts far removed from the central nervous system found at autopsy of individuals who succumbed to the disease within twenty-four hours of its inception, and finally the appearance of characteristic lesions in the eye synchronously with manifestations referable to the central nervous system, all point to an early generalization of the meningococci, but are not competent to prove that such an infection antedated the meningeal involvement.**

The experimental study of this problem has not yet yielded decisive results. Bettencourt and Franca[6] failed to produce meningitis in monkeys either by rubbing cultures of the meningococcus into the nasal mucous membrane or by intravenous injection.

Flexner[31] succeeded in producing meningitis in monkeys by intraspinal injection, the resulting meningitis having in this case also the basal distribution thought suggestive of nasopharyngeal infection.

Elser and Huntoon, by intravenous injections of *Streptococcus mucosus* in rabbits succeeded in producing a meningitis which in its onset and the distribution of lesions resembled the meningococcus meningitis of man.

Finally, we may say that the evidence at our command at present strongly suggests that the primary infection in epidemic cerebrospinal meningitis is respiratory, in most cases nasopharyngeal, and that the meningeal infection is developed through the blood.

Protection of the community therefore will demand not only the isolation of those sick with the epidemic disease, but the detection of the many unaffected "carriers." To what extent this may be practicable remains to be seen. In the restricted fields offered by regimental organizations, the German military officers have already applied these methods with apparent success.

The efforts to free carriers from their infection (nasopharyngeal) have, so far as I can learn, proved ineffective. Various applications, douches and insufflations have been tried without success. In this regard the experience seems to repeat that with diphtheritic infections of the throat. In time the infection appears to die out in most cases, but treatment does not hasten that desired end.

Our present knowledge would suggest the desirability of treating these persons by serum or vaccines. The possibility of protecting the exposed by like means naturally presents itself, but thus far I have not been able to learn of any work along these lines.

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